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# American Journal of Obstetrics and Gynecology

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## Original Communications

### THE HARMFUL INFLUENCE OF PREGNANCY ON ADVANCED TUBERCULOSIS AS MODIFIED BY COLLAPSE THERAPY\*

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*(From the Wawa Chest Hospital, Wawa, Pa.)*

IT IS generally recognized that in a significant number of patients pregnancy can have a harmful influence on the evolution of tuberculosis. This may become clinically manifest during the early months of pregnancy or during the post-partum period and may endanger the life of the mother. Many women trace the clinical onset of their tuberculosis to a period during pregnancy or following delivery; therefore, the combination of tuberculosis and pregnancy continues to be a subject of critical interest.<sup>1-4</sup> Although it is appreciated that pregnancy in the tuberculous woman is a matter of carefully judging many factors (physiologic, social, economic, as well as pathologic), two general rules have been laid down for the guidance of females afflicted with advanced tuberculosis: (1) Women with advanced tuberculosis should not marry; (2) Married women with advanced tuberculosis should not conceive. This is especially true if there has been recent activity.

Since collapse therapy has unquestionably improved the outlook of the tuberculous patient in general, it is of prime importance to re-evaluate the prognosis of the parturient woman with advanced tuberculosis under conditions of modern therapy to determine to what extent the above mentioned views need modification. There are increasing reports of women with advanced tuberculosis who have come through one or more pregnancies without harm once the disease in the lungs was successfully controlled with pneumothorax or thoracoplasty, or some other form of collapse therapy.<sup>5-9</sup>

\*Presented before The Obstetrical Society of Philadelphia, December 3, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The present study is an effort to determine the immediate and long-term effects of pregnancy, and the responsibilities which follow, upon advanced tuberculous in a single consecutive series of twenty-six white women who received collapse therapy to control the tuberculosis, before giving birth to one or more children. The collapse therapy procedures employed to control the tuberculosis in this series were: pneumothorax—unilateral (20), bilateral (6), pneumolysis (7), maintenance oleothorax (7), and phrenic nerve interruption (6), in various combination. These patients have been under constant clinical and roentgenologic observation for varying periods during the past fifteen years. The minimum period of observation has been sixteen months; the maximum, fifteen years; the average for the group was approximately nine years.

### Description of Material

All were private patients of about the same social and economic level. I know the great majority of these patients intimately and have kept accurate and detailed notes with repeated fluoroscopic and x-ray studies. They were cooperative and interested in their health. With stated exceptions, they undertook marriage and pregnancy only after careful consideration and at a time when they had every reason to feel reasonably secure in their health. Their intelligence and morale were on a higher plane than that usually encountered in clinic patients. Pregnant white and colored women receiving collapse therapy in the clinic, and pregnant tuberculous women who received no collapse therapy, are not included in this presentation. These are points worth stressing; for, in a sense, by limiting the study to such a selected group, the results should represent generally the more favorable side of the combination of pregnancy and tuberculosis.

With one exception (Case 23, Fig. 6), all patients had cavity formation and tubercle bacilli in the sputum when first seen. In nine, the disease was unilateral; in six, predominantly unilateral; and in eleven, it was definitely advanced in both lungs. Ten of these women were married and sixteen were single when first seen, but the latter group subsequently married and reared families. Twenty-two women were primiparas and four multiparas when first placed under treatment for tuberculosis. These women had forty-eight known pregnancies following the establishment of collapse therapy and gave birth to forty children.

Fifteen women gave birth to one child, nine to two children, one to three children (one set of twins) and one to four children. The other pregnancies terminated in four abortions and five miscarriages. The average period of observation after the first pregnancy was—58 months, second pregnancy—41 months, third pregnancy—45 months, and after the fourth pregnancy—12 months. The women received their obstetrical care at the hands of twenty different obstetricians. None of the women nursed their babies.

These cases fall into three groups: 1. Patients in whom tuberculosis was recognized and treated successfully with collapse therapy before pregnancy—22 cases. 2. Patients in whom the tuberculosis was recognized, but treated unsatisfactorily with collapse therapy (inability to close cavities) before pregnancy set in—3 cases. 3. Patients in whom the tuberculosis was first recognized during pregnancy—2 cases (one of

these patients received pneumothorax, subsequently became pregnant, and is again considered in group 1 as a new case).

### Patients in Whom Tuberculosis Was Recognized and Treated Successfully With Collapse Therapy Before Pregnancy

Twenty-two patients with advanced tuberculosis were successfully treated with collapse therapy before becoming pregnant. Two to twenty-seven months elapsed before the tuberculosis was stabilized by the collapse and the sputum was rendered free of tubercle bacilli. The average for the group was 5.5 months. An additional 8 to 26 months elapsed from stabilization of the tuberculosis and disappearance of tubercle bacilli from the sputum to the termination of the first pregnancy, with an average for the group of 13 months. Approximately 40 months elapsed between the first and second pregnancies and 27 months between the third and fourth pregnancies. In the case of the sixteen women who were single when first seen, 29 months elapsed on the average from stabilization of the disease and negative sputum to date of marriage. It is apparent from these figures that, with the one exception noted below, marriage and pregnancy were undertaken only after careful consideration at a time when there was ample justification to regard the tuberculosis as arrested or "cured" according to accepted standards. Notwithstanding these precautions, there was evidence of increased disease in 4, or 18 per cent of the group, as a direct result of pregnancy.

In three of the four patients, increased disease, of sufficient clinical importance to require treatment—bed rest in one, and pneumothorax therapy in two, first became evident within two months *following* childbirth. All three responded to treatment and did well. The fourth patient developed increased disease during the *early months* of a pregnancy which terminated spontaneously at three months. The increased disease produced no ill effects and required no special treatment. It underwent spontaneous retrogression upon termination of pregnancy.

A detailed discussion of the various subgroups, comprising these twenty-two patients, is in order.

(a) In nine patients (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9), the disease was confined to one lung when first seen with no x-ray evidence of tuberculosis in the contralateral lung. All received pneumothorax therapy (in four cases, Figs. 4, 5, 8, 9, the pneumothorax was later replaced with maintenance oleothorax). In each instance, all cavities were closed, the positive sputum rendered negative, and the patient restored to good health before pregnancy set in. All nine did well and their clinical course was entirely uneventful.

Four of these patients (Figs. 5, 6, 7, 9) had one pregnancy and one baby each, of which one baby died at premature birth at eight months. One patient (Fig. 9) is pregnant a second time. Three patients (Figs. 1, 2, 4) had two pregnancies and two healthy babies each. One (Fig. 3) had three pregnancies, the first of which was a miscarriage at two months. Her other two pregnancies were full term and resulted in two healthy babies. One patient (Fig. 8) had three pregnancies, the first two of which were miscarriages at two months each and the third was entirely normal, resulting in the birth of a healthy girl. This patient, incidentally, had a double vagina and uterus.

(b) In five patients (Figs. 10, 11, 12, 13-15, 16-18), the disease was confined almost entirely to one lung, but there was x-ray evidence of tuberculosis in the contralateral lung, considered of no clinical importance at the time and consisting for the most part of moderately dense spots and

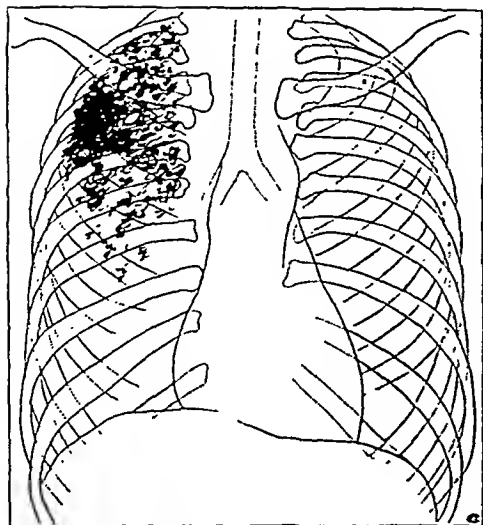


Fig. 1.—Case 1.

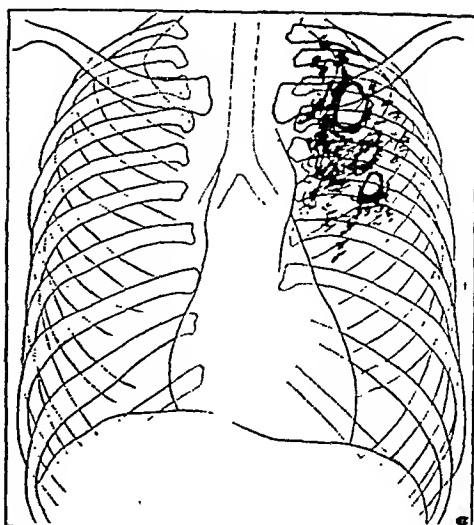


Fig. 2.—Case 5.

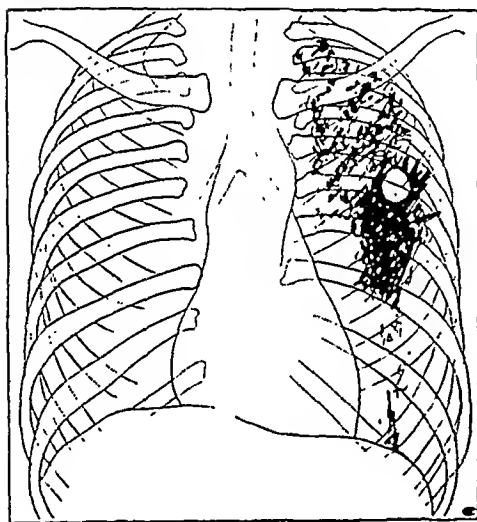


Fig. 3.—Case 11.

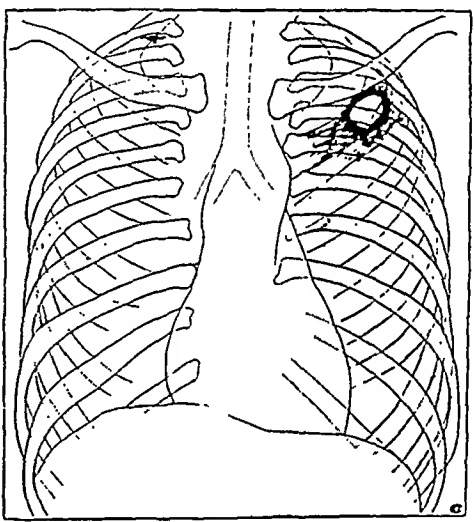


Fig. 4.—Case 18.

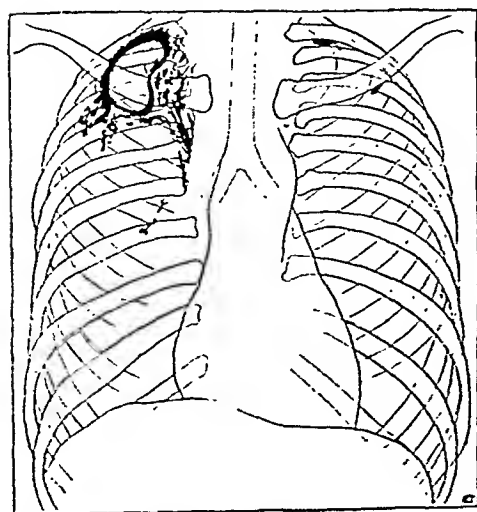


Fig. 5.—Case 19.

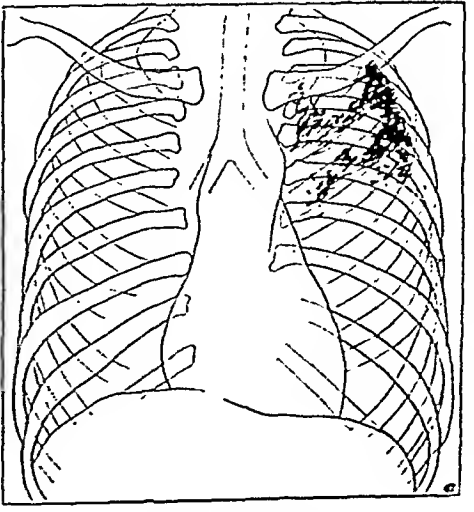


Fig. 6.—Case 23.

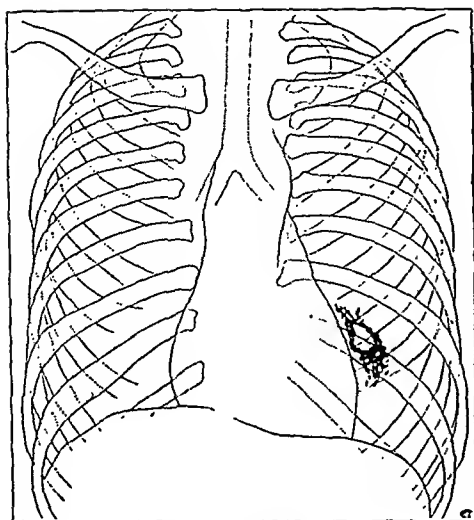


Fig. 7.—Case 24.

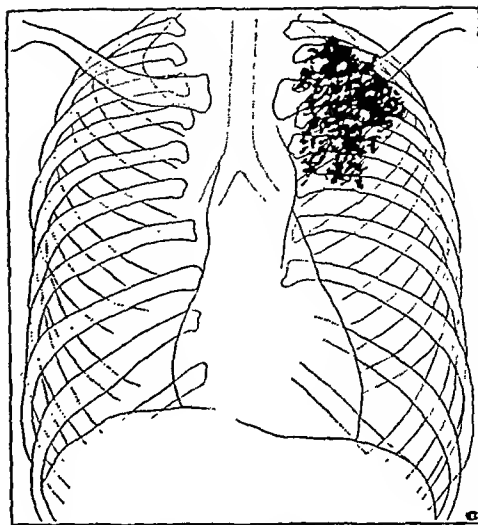


Fig. 8.—Case 25.

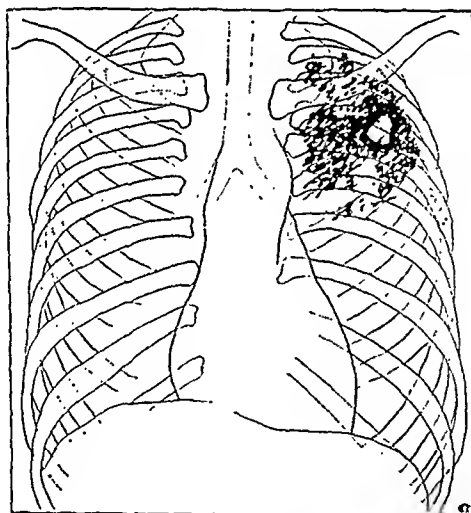


Fig. 9.—Case 26.

**Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy\***

*Group a.*—Cases 1, 5, 11, 18, 19, 23, 24, 25, and 26 (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9). Under observation since July 23, 1928, July 28, 1929, July 14, 1932, June 30, 1936, July 17, 1936, July 26, 1936, March 2, 1938, April 8, 1938, March 23, 1939, respectively.

In these patients the disease was confined to one lung when first seen with no x-ray evidence of tuberculosis in the contralateral lung. All received pneumothorax therapy. In each instance all cavities were closed, the positive sputum rendered negative, and the patient restored to good health before pregnancy set in. All women did well and their clinical course was entirely uneventful.

\*Cases are numbered consecutively in the order in which they presented themselves for treatment.

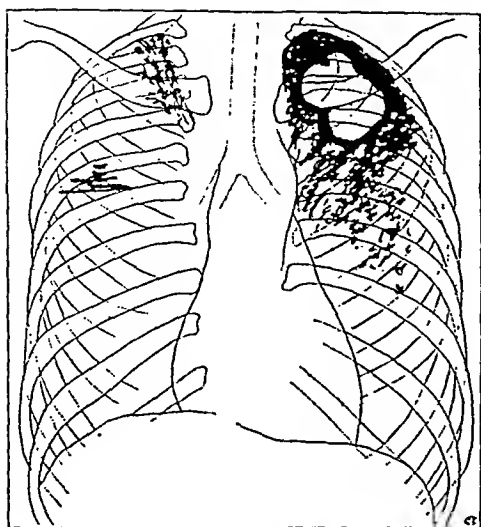


Fig. 10.—Case 14.

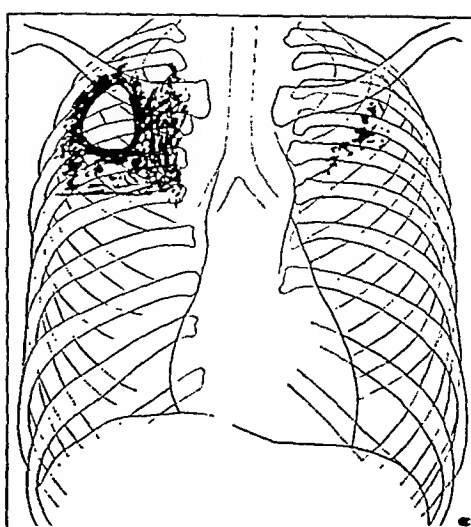


Fig. 11.—Case 15.

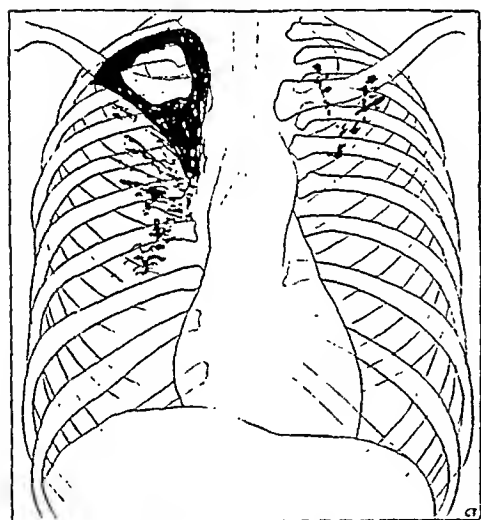


Fig. 12.—Case 16.

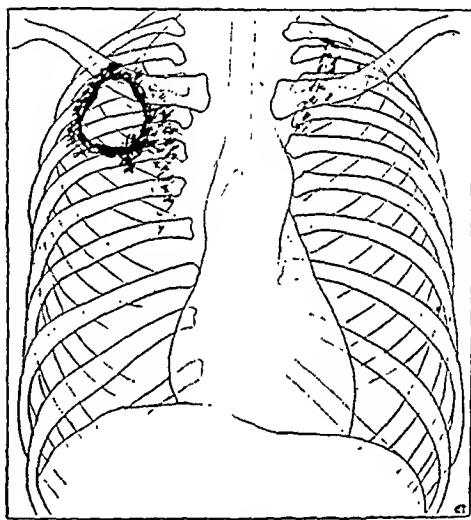


Fig. 13.—Case 3.

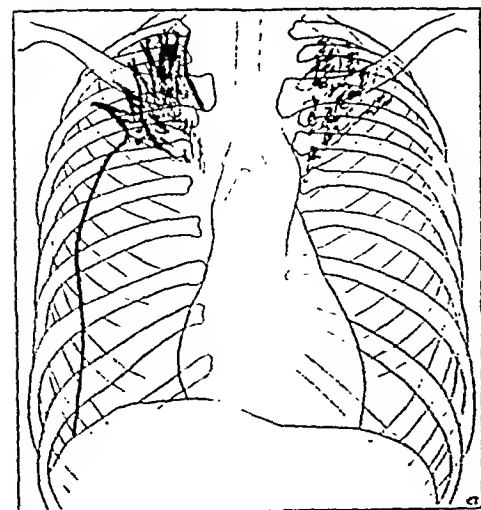


Fig. 14.—Case 3.

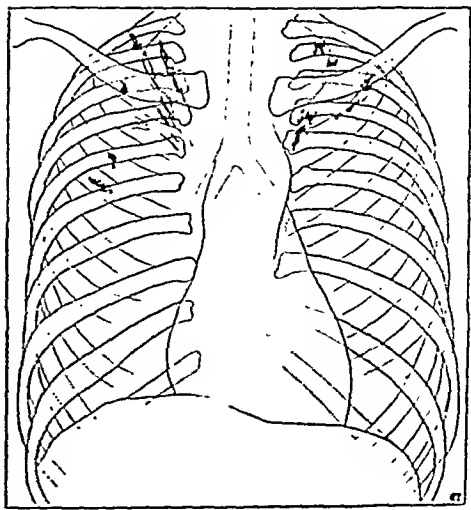


Fig. 15.—Case 3.

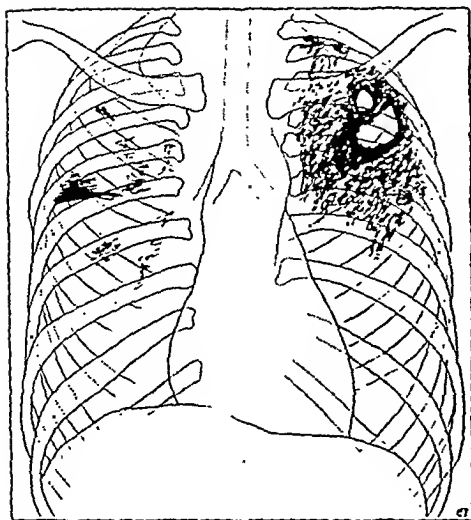


Fig. 16.—Case 10.

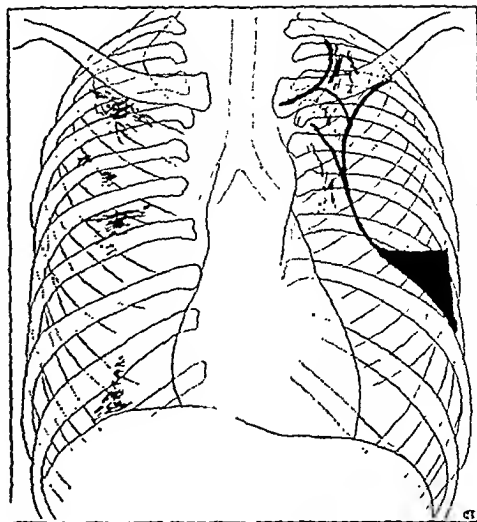


Fig. 17.—Case 10.

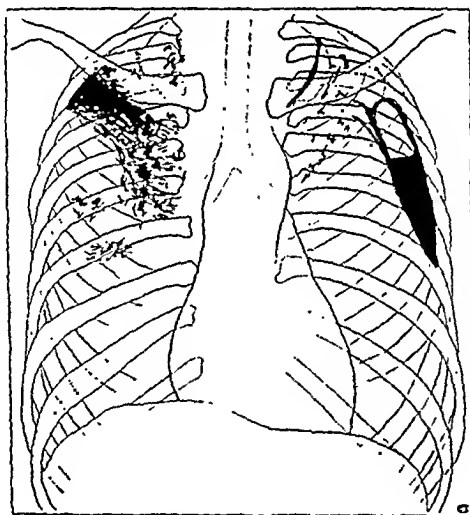


Fig. 18.—Case 10.

**Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy**

*Group b.*—Cases 14, 15, and 16 (Figs. 10, 11, and 12); Cases 3 (Figs. 13, 14, 15) and 10 (Figs. 16, 17, 18). Under observation since November 20, 1933, July 21, 1934, April 28, 1935; June 28, 1929 and June 1, 1932, respectively.

In these patients the disease was confined almost entirely to one lung, but there was x-ray evidence of tuberculosis in the contralateral lung, considered of no clinical importance at the time and consisting for the most part of moderately dense spots and fibrous strands. Only the disease in the more involved lung was treated with pneumothorax therapy before pregnancy set in. In every instance the disease was well controlled in both lungs, with all cavities closed, and the sputum rendered negative long before pregnancy.

Three of the five patients (Cases 14, 15, and 16; Figs. 10, 11, and 12) did well and had an uneventful clinical and roentgenologic history.

Two of the five patients (Case 3; Figs. 13, 14, and 15 and Case 10; Figs. 16, 17, and 18) had definite x-ray evidence of new disease in the "good" lung as a direct result of the pregnancy. In Case 3, this occurred two months following delivery (Fig. 14) but underwent spontaneous reabsorption (Fig. 15). In Case 10, new disease (Fig. 17), gradually became worse during time pneumothorax therapy was instituted to bring the disease under control.



fibrous strands. Only the disease in the more involved lung was treated with pneumothorax therapy before pregnancy set in. In two (Figs. 11, 12), the pneumothorax was supplemented with a pneumonolysis operation and the pneumothorax later replaced with maintenance oleothorax. In every instance, the disease was well controlled in both lungs, with all cavities closed, and the sputum rendered negative long before pregnancy.

Three of the five patients (Figs. 10, 11, 12) did well and had an uneventful clinical and roentgenologic history. Two of these three patients (Figs. 10, 11) had one pregnancy and one healthy baby each; one of them (Fig. 10) is pregnant a second time. The third patient (Fig. 12) had three pregnancies, the first of which was terminated artificially at two months because of an unreasonable fear on the part of the patient of what the pregnancy might do to the tuberculosis. The second and third pregnancies were full term and uneventful and resulted in two healthy children.

Two of the five patients (Figs. 13-15 and 16-18) had definite x-ray evidence of new disease in the "good" lung as a direct result of the pregnancy. In one patient (Figs. 14 and 15), this occurred two months following delivery. The new disease was not accompanied by clinical signs or symptoms and would not have been detected except for the x-ray. The disease subsided spontaneously and no therapy was required. The patient suffered no ill effects. In the other patient (Figs. 16-18) an increase in disease in the "good" lung was first noted in the x-ray film three weeks after the birth of the second baby (the first pregnancy was entirely uneventful) but at the time gave rise to no signs or symptoms and apparently required no treatment. It was entirely an x-ray observation. Gradually, however, the disease in the "good" lung became sufficiently important clinically to warrant pneumothorax treatment. This patient has done well with bilateral pneumothorax therapy and at present (three years after all pneumothorax treatment has been discontinued) is enjoying excellent health.

(c) In three patients (Figs. 19, 20, 21), the disease was bilateral, but advanced in both lungs. These patients were treated successfully with bilateral pneumothorax therapy. In two the pneumothorax was made complete with pneumonolysis and later replaced with bilateral maintenance oleothorax before the patients became pregnant. All did well and their clinical course was entirely uneventful. Two of these patients (Figs. 20 and 21) had one pregnancy and one baby each, the third (Fig. 19) had three pregnancies and two healthy babies. Her second pregnancy was terminated artificially at two months.

(d) In three patients (Figs. 22, 23, 24-26), the disease was bilateral and advanced in both lungs. Before the patients became pregnant, the lungs were treated successfully with pneumothorax therapy on the more involved side and with phrenic nerve interruption on the other. In all instances, the tuberculosis in the two lungs was definitely controlled and the sputum was negative many months before pregnancy set in. Two (Figs. 22, 23) had an entirely uneventful tuberculosis history following pregnancy. One of these two patients (Fig. 22) had four pregnancies and four living children; the other patient (Fig. 23), two pregnancies, the first of which was full term and the second an abortion at two months.

The third patient in this subgroup (Figs. 24-26) had four pregnancies. She had an extension of the disease in the lung treated with phrenic nerve interruption during the early months of the third preg-

naney. Her first pregnancy was entirely uneventful and she gave birth to a full-term baby. The second pregnancy terminated spontaneously at eight months in the birth of twins. Both children died shortly after birth, but the mother's health remained good. During the first two months of the third pregnancy, there was found in the lung previously treated successfully with phrenic nerve interruption x-ray evidence of increased disease, sufficiently serious to require bed rest treatment for several months. However, this pregnancy terminated spontaneously at three months and the tuberculosis quieted down almost at once. Six months later, this patient again became pregnant, again had a miscarriage at three months, but without harmful effect on the tuberculosis. Only during the third pregnancy was there evidence of increased disease and this in the lung treated with phrenic nerve interruption.

(e) In two patients (Figs. 27 and 28-30), the disease was bilateral and advanced in both lungs when first seen. Pneumothorax was used successfully on the more involved side and no collapse therapy whatever was used on the other side before pregnancy set in. In one of these (Fig. 27), the disease in the contralateral lung responded so well to bed rest treatment during the time required to control the disease in the worse lung with pneumothorax, that bilateral collapse therapy was not considered necessary. This patient went through three pregnancies. The first two were full term and the third was an abortion at two months. Her clinical course was entirely uneventful.

The other patient (Figs. 28-30) became pregnant unexpectedly two months after pneumothorax was instituted on the right or more involved side at a time when the disease was not considered stabilized in either lung. The danger of the pregnancy activating the tuberculosis, particularly in the uncollapsed lung, was fully appreciated; but after careful consideration, the patient, who was anxious to have the child, was permitted to go to term with the understanding that bilateral collapse therapy might be necessary. She was kept on bed rest throughout the entire pregnancy and treated as if she had active tuberculosis. In due course, with nothing unusual happening, she was delivered of a healthy male baby. An x-ray, four weeks after delivery, showed no change in the character of the disease. Two months later, however, there was a very definite spread of the tuberculosis in the left or uncollapsed lung and clinical symptoms of active disease made their appearance. Bilateral pneumothorax was promptly instituted and the disease controlled. This patient is still receiving bilateral pneumothorax—six years later—and is leading a normal active life, works, and helps to support the family. The baby is healthy.

#### **Patients in Whom the Tuberculosis was Recognized but Treated Unsatisfactorily (Inability to Close Cavities) Before Pregnancy**

Three patients in this series (Figs. 31, 32, 33) received collapse therapy, but the cavities were not closed nor the sputum rendered free of tubercle bacilli at the beginning of pregnancy. Not one of these patients did well. One is dead, one is in poor health, and the other, when last observed (October 28, 1936), was considered a hopeless case of tuberculosis. In two of these patients, the pregnancy was not immediately followed by an increase in the disease, but the fact remains that they were all doing well prior to pregnancy and began doing poorly sometime after childbirth.

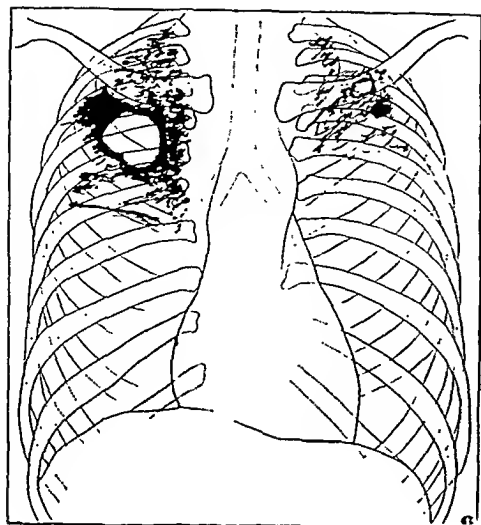


Fig. 19.—Case 6.

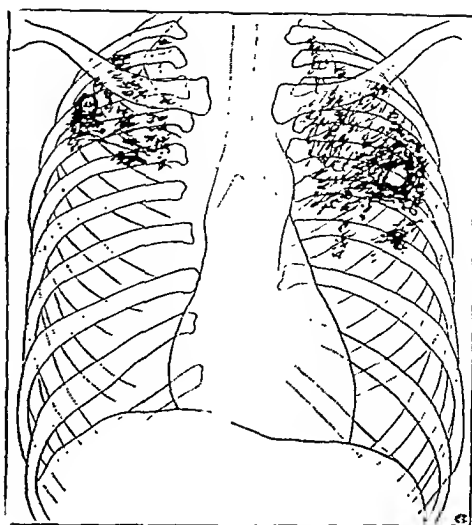


Fig. 20.—Case 21.

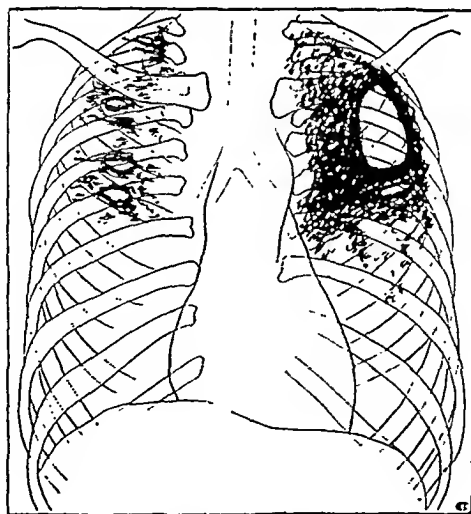


Fig. 21.—Case 22.

**Patients in Whom Tuberculosis Was Recognized and Treated Successfully  
with Collapse Therapy Before Pregnancy**

*Group c.*—Cases 6, 21, and 22 (Figs. 19, 20, and 21). Under observation since September 20, 1930, April 2, 1937, and April 5, 1937, respectively.

In these patients the disease was bilateral, but advanced in both lungs. All three were treated successfully with bilateral pneumothorax therapy before the patients became pregnant. All did well and their clinical course was entirely uneventful.

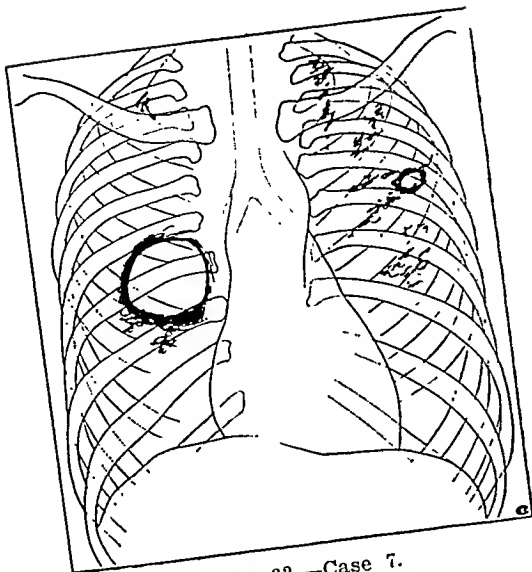


Fig. 22.—Case 7.

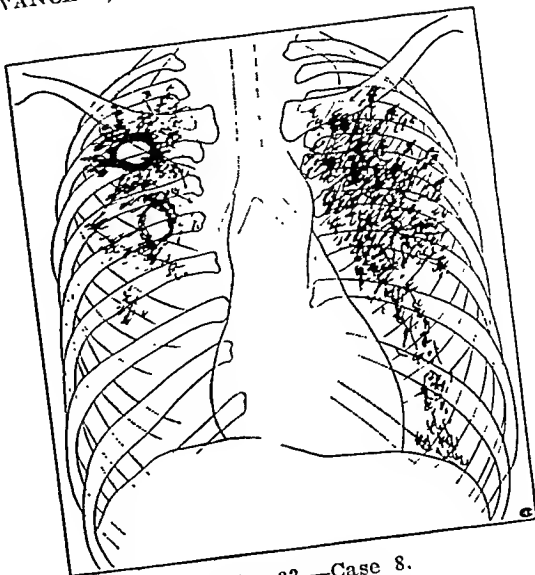


Fig. 23.—Case 8.

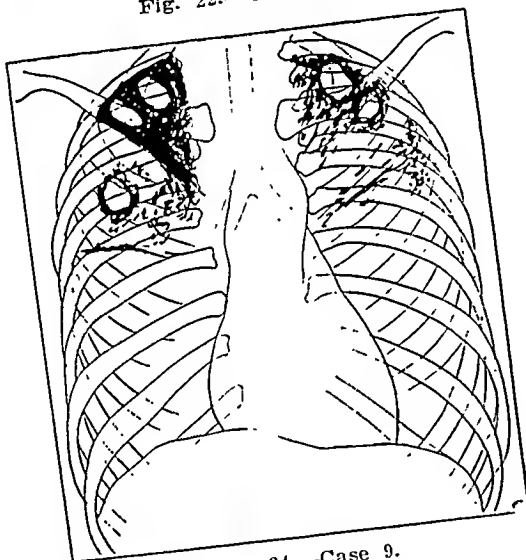


Fig. 24.—Case 9.

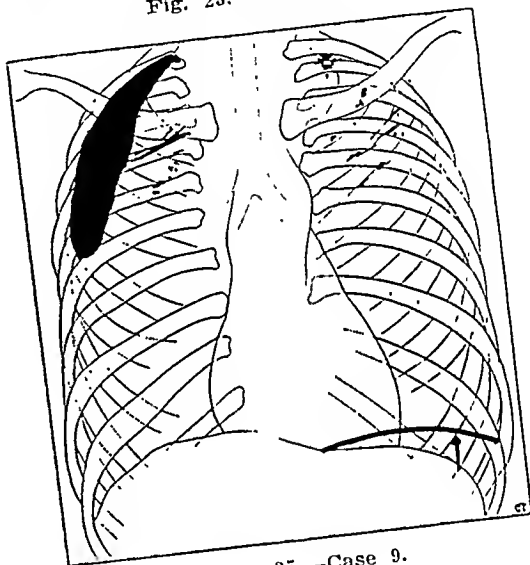


Fig. 25.—Case 9.

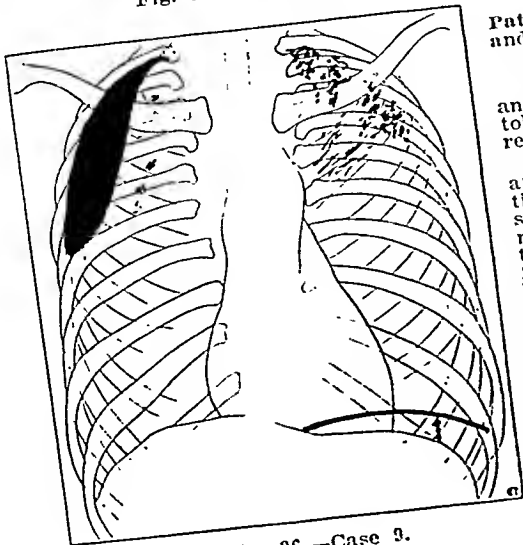


Fig. 26.—Case 9.

**Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy**

Group d.—Cases 7, 8, and 9 (Figs. 22, 23, and 24, 25, 26). Under observation since October 7, 1930, April 17, 1931, and May 20, 1932, respectively.

In these patients the disease was bilateral and advanced in both lungs. Before the patients became pregnant, the lungs were treated successfully with pneumothorax therapy on the more involved side and with phrenic nerve interruption on the other. Cases 7 and 8 (Figs. 22 and 23) had an entirely uneventful tuberculosis history following pregnancy.

In Case 9 (Figs. 24, 25, and 26), there was extension of disease in the lung treated with phrenic nerve interruption during the early months of the third pregnancy (Fig. 26—pregnant six weeks), sufficiently serious to require bed rest treatment for several months. The other pregnancies were entirely without effect on the tuberculosis (Fig. 25, one month after first miscarriage and twenty-five months after second delivery).

In retrospect, the disease in each instance was neither more intense nor more extensive when first seen than in some of the patients in whom adequate collapse could be established before pregnancy set in. These three patients serve as excellent controls and reveal in striking contrast the risk of pregnancy to women with advanced tuberculosis not previously controlled with adequate collapse therapy. The case histories follow:

Case No. 17 (Fig. 33), W. H., aged 28, first consulted me on January 22, 1935, but was known to have had tuberculosis since 1926. Following the diagnosis in 1926, she was "cured" without collapse therapy and later worked as a nurse in a sanatorium for about two years and made a fair clinical recovery. In 1929, she married and in 1930 gave birth to a baby without any apparent ill effects. She maintained reasonably good health until the birth of the second baby in August, 1933. She has not been well since. At first, she returned to "bed rest" and although she regained twenty-seven pounds, she continued to cough and expectorate and at times would expectorate blood. In January, 1935, I instituted pneumothorax therapy on the left side and on May 25, 1935, crushed the right phrenic nerve. There was gratifying and continued clearing of the disease in both lungs during the following months as a direct result of the collapse therapy, but one cavity in the upper part of the left lung, although reduced in size, failed to close because of extensive inoperable adhesions. In October, 1935, she became pregnant. Therapeutic abortion was advised, but the patient refused on religious grounds so there was nothing to do but carry her to term. Unfortunately, she did not do at all well and her health went steadily down with each passing month of pregnancy. On April 17, 1936, she gave birth to a premature infant of seven months, who died within a few hours. The mother died of progressive tuberculosis one month later. There is no question in my mind that the pregnancy was the one deciding factor which immediately altered her prognosis for the worse.

Case No. 13 (Fig. 32), C. D., aged 22. This patient traced the onset of her tuberculosis to her last pregnancy. She became ill in 1932 with respiratory symptoms, which never left her, six weeks after giving birth. She was referred to me on April 27, 1933, and at that time there was extensive involvement of the entire right lung with several cavities present. There was also disease in the left lung limited to the middle third and consisting of grouped flocculent spots, but no cavities. She weighed eighty pounds and was in poor health. Pneumothorax therapy was established on the right and she was kept in bed. There followed striking and rapid improvement during the next five months so that by November, 1933, she weighed ninety-nine pounds and her cough and expectoration were definitely reduced. The disease in the left lung was noticeably better, but one cavity in the right upper lobe could not be closed with the pneumothorax because of extensive inoperable adhesions. In the light of subsequent events, November, 1933, was the peak month of improvement. During the next year, she just about held her own, with the cavity in the right apex remaining open. It was under these circumstances that she became pregnant, nineteen months after pneumothorax was instituted. She refused an abortion and on September 21, 1935 gave birth to a healthy baby girl. As determined by x-ray, there was no apparent damage to the lungs for at least three months following childbirth. Clinically, however, she was never the same. Her health gradually dwindled. By May, 1936, there was more disease in the left

lung, the uncollapsed cavity in the right apex was larger, her weight was reduced to eighty-one pounds, and the prognosis was considered hopeless. Her condition was no better when I saw her last on October 28, 1936. Here, again, there is no question but that the prognosis remained reasonably good until she became pregnant and that it became virtually hopeless following delivery. The only difference in this case as contrasted with some of the patients who did well during and after pregnancy was in the quality of the collapse. Her disease was not anatomically well controlled with the pneumothorax when she became pregnant.

Case No. 12 (Fig. 31), M. W. This patient, aged 26, was known to have had tuberculosis as far back as 1928. I first saw her on July 8, 1932. At the time there was involvement of both lungs, limited to the upper lobes with a cavity at the right apex. The disease was moderately active. Pneumothorax was instituted on the right side, but was ineffectual in closing the cavity. This treatment was abandoned and replaced with a temporary phrenic nerve interruption. She improved steadily during the next year, regained much of her previous health and moved to another city. The cavity at the right apex, although smaller, was still present. In 1938, her only child, a boy eleven years old, was drowned and she decided to have another baby. She was apparently in good health and her doctor assured her it was safe. She vomited a great deal during the early months of pregnancy and lost about twenty-five pounds. In spite of this, her general health apparently remained good, and on May 17, 1939, she gave birth to a healthy baby. Her health remained apparently unchanged until March, 1941, when the tuberculosis became definitely active and she again consulted me on July 18, 1941. At the time, there was a large cavity at the right apex much larger than in 1932. The disease in the left lung, however, appeared healed and consisted, for the most part, of calcified spots. Unfortunately, there are no serial x-ray studies available before and after childbirth, but it is fair to assume from the very nature of the case that the cavity was open all through pregnancy. On close questioning, she did not have "good health" following childbirth, and it is quite probable that her tuberculosis gradually became worse following the birth of the baby. The disease was of the chronic, fibro-ulcerative type with relatively few symptoms. Many months must have elapsed before the cavity reached the size it ultimately did when she again consulted me. At present, this patient is going from bad to worse and will most certainly die of tuberculosis. This case, again, illustrates the unfavorable influence of pregnancy on advanced tuberculosis, not adequately controlled with collapse therapy. Phrenic nerve interruption is not enough.

### **Patients in Whom Tuberculosis Was First Recognized During Pregnancy**

The diagnosis of clinically active tuberculosis and pregnancy always presents a serious problem, requiring prompt and energetic action. The course of the disease is often markedly aggravated and the tuberculosis may constitute a real threat to life. The accepted procedure in such cases is therapeutic abortion, during the first trimester; or, if the patient presents herself near the stage of fetal viability or close to term, careful medical and obstetric supervision, modified as individual requirements may dictate.

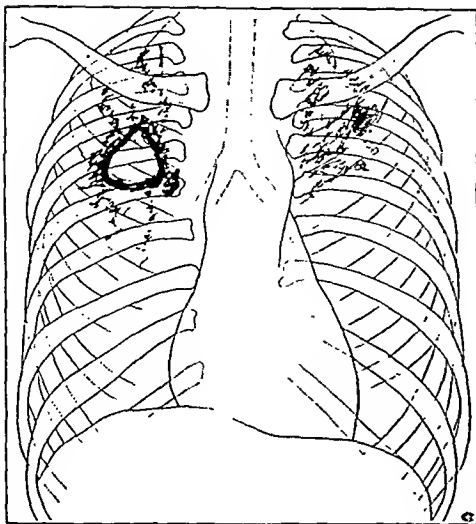


Fig. 27.—Case 4.

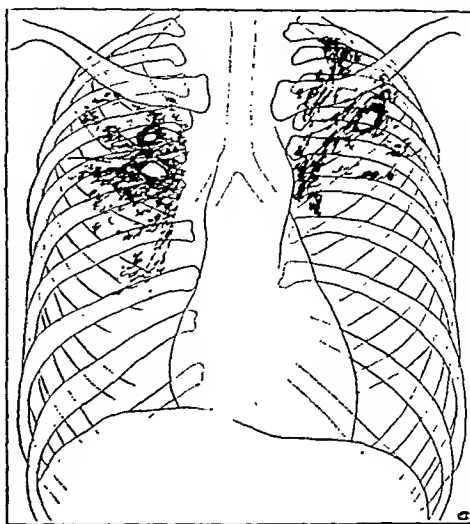


Fig. 28.—Case 20.

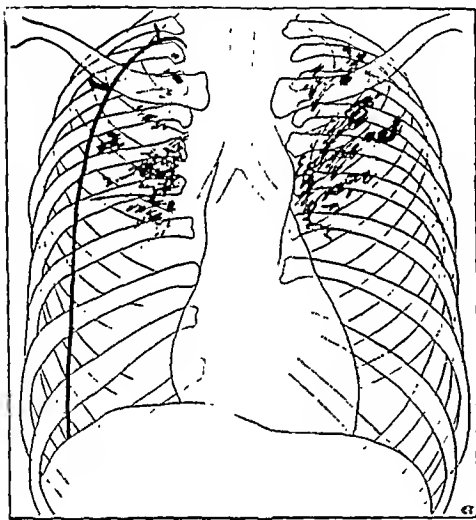


Fig. 29.—Case 20.

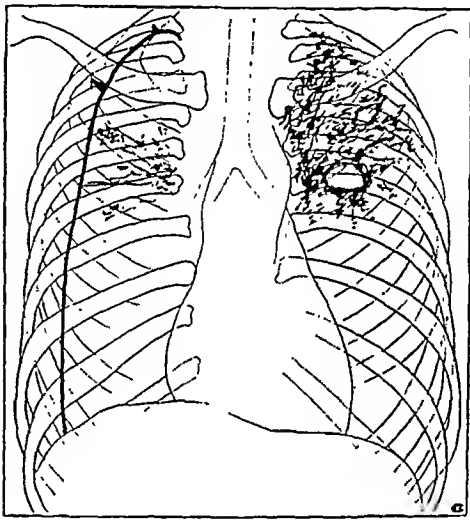


Fig. 30.—Case 20.

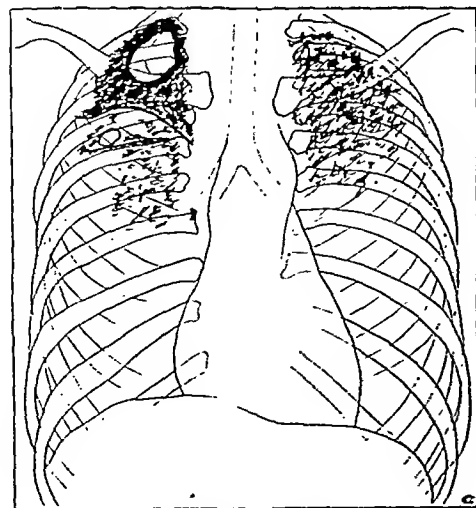


Fig. 31.—Case 12.

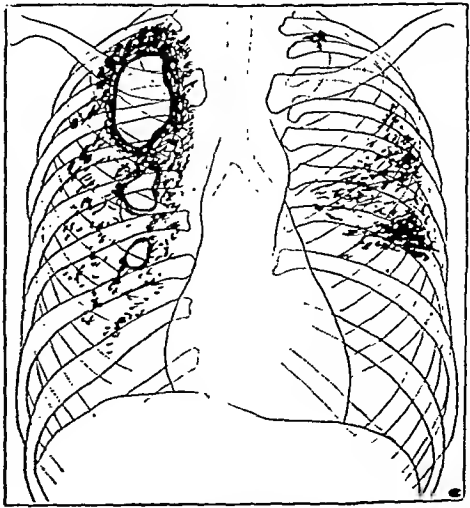


Fig. 32.—Case 13.

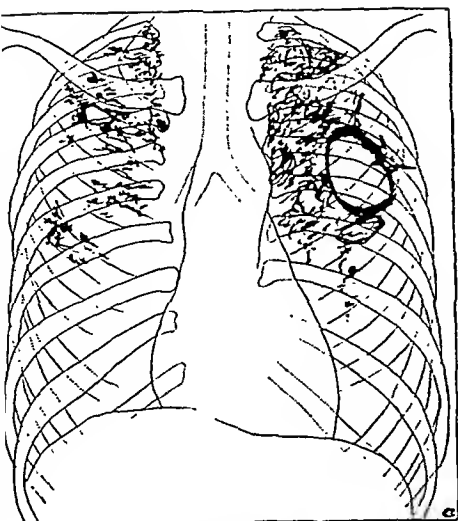


Fig. 33.—Case 17.

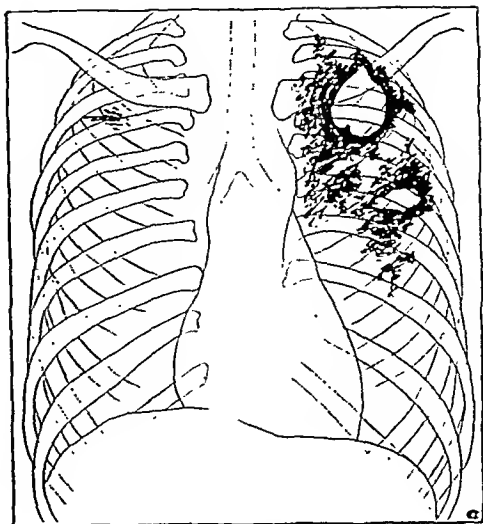


Fig. 34.—Case 2.

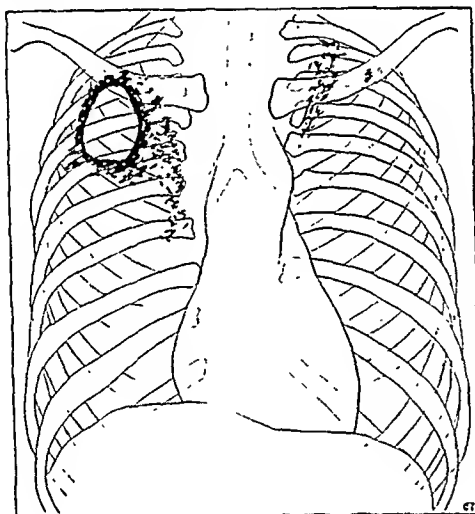


Fig. 35.—Case 3.

**Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy**

*Group c.*—Cases 4 and 20 (Figs. 27, and 28, 29, 30). Under observation since June 8, 1929 and October 24, 1936, respectively.

In these patients the disease was bilateral and advanced in both lungs when first seen. Pneumothorax was used successfully on the more involved side and no collapse therapy whatever on the other side before pregnancy set in. In Case 4 (Fig. 27), the clinical course was entirely uneventful; in Case 20, (Figs. 28, 29, and 30), new disease appeared in the untreated lung two months after delivery and required pneumothorax therapy (Fig. 30). Fig. 29 shows the condition of the lungs when the patient was four months pregnant.

**Patients in Whom the Tuberculosis Was Recognized but Treated Unsatisfactorily Before Pregnancy**

Cases 12, 13, and 17 (Figs. 31, 32, and 33). Under observation since July 8, 1932, April 5, 1933, and January 22, 1935, respectively.

In these patients the cavities were not closed and the sputum rendered free of tubercle bacilli before pregnancy set in. All did poorly. For details, see text.

**Patients in Whom Tuberculosis Was First Recognized During Pregnancy**

Cases 2 and 3 (Figs. 34 and 35). Under observation since July 28, 1928 and June 28, 1929, respectively.

Case 2 (Fig. 34) was treated with artificial pneumothorax and no interference with pregnancy; Case 3 (Fig. 35), with therapeutic abortion, followed by pneumothorax therapy. Both patients did well.



Two patients in this series (Cases 2 and 3, Figs. 34 and 35) had active, advanced tuberculosis, first recognized during pregnancy. One was treated with therapeutic abortion, followed by pneumothorax therapy; the other, by immediate pneumothorax and no interference with pregnancy. Both patients did well. It is therefore of interest to present these cases in some detail.

Case No. 2, R. S., aged 22, first came under my observation on July 20, 1928, suffering with advanced active tuberculosis of the left lung with cavity formation and sputum positive for tubercle bacilli. Râles were heard to the fourth rib, anteriorly. The patient also complained of nausea and vomiting with pain over the right lower abdomen, and no menses for the past two months. These symptoms, however, received little consideration at the time and were believed to be due to probable ileocecal tuberculosis. The patient was placed on calcium chloride therapy intravenously and in due time the nausea and vomiting disappeared. During the first six weeks of observation the temperature, cough, and expectoration continued to increase in severity and the patient was losing steadily in weight. On September 1, 1928, artificial pneumothorax was instituted on the left side and almost immediately the patient began to show definite improvement. Temperature and pulse soon returned to normal, cough and expectoration were greatly reduced, and tubercle bacilli disappeared from the sputum. The patient began to gain in weight and naturally felt greatly elated over the turn of events. On November 8, 1928, the patient called my attention to the fact that her abdomen was increased in size and made the suggestion that she was pregnant. Careful examination soon confirmed the diagnosis and for the first time it was realized that the patient was pregnant when first seen and that the nausea and vomiting were not due to probable ileocecal tuberculosis, as was first believed, but to pregnancy. Of course, it was too late to interrupt gestation, and again the patient was in such splendid shape clinically, that she was advised to go through with it. Everything went along smoothly until January 10, 1929, when she suddenly developed high fever of 104 degrees with moderate pain in the right upper abdomen. A diagnosis of right-sided pyelitis was established and the patient treated accordingly with satisfactory results. At the same time, fluid appeared in the left pleural cavity, which required several aspirations. On March 4, 1929, the patient delivered a healthy male child. The convalescence was uneventful. Although the sputum became positive for a short time after the delivery, the tubercle bacilli again disappeared. The patient continued to gain in weight and strength and left my care as an arrested case of tuberculosis on July 16, 1929. The last report from the patient in 1932 stated that she was enjoying good health, that the baby was in splendid condition, and that she was still continuing with artificial pneumothorax treatment.

It is highly probable that had I realized that this patient was pregnant when she first came under my care, she would have been aborted.

Case No. 3, I. G., aged 24, first came under observation for tuberculosis in May, 1929, at which time she was known to be three months pregnant. Both x-ray and physical findings revealed softening and excavation of the right upper lobe. The sputum was positive for tubercle bacilli and clinically, there were cough, expectoration, fever, and night sweats. During the two weeks prior to the diagnosis of tuberculosis, the patient had lost nine pounds in weight and was confined to bed. Because of the severe character and apparent acute onset of the tuberculosis, a

therapeutic abortion was performed on June 1, 1929. My contact with the patient began on June 19, 1929. The patient was still manifesting all the signs and symptoms of acute tuberculosis, and artificial pneumothorax was instituted on the right side. In a short time, her temperature returned to normal, cough and expectoration practically disappeared, and her weight picked up steadily. Subsequently, she had two children while under pneumothorax treatment (discussed along with patients in group one).

This experience certainly raises the question of the wisdom of abortion in all cases of active tuberculosis and pregnancy without first considering artificial pneumothorax. If a good anatomical collapse can be obtained, and this can often be determined within a month or two, the patient can be permitted to go to term. Even thoracoplasty has been done successfully during pregnancy.<sup>9</sup>

### Discussion

One striking feature emerges from a study of these twenty-six case histories, namely, the freedom from reactivation of advanced tuberculosis in a lung, the diseased area of which was anatomically well collapsed before pregnancy. Every exacerbation or extension of disease in this series was always in the lung not collapsed, poorly collapsed, or treated with phrenic nerve interruption. The extent and severity of the original disease, whether confined to the right or left lung, or both lungs, were not determining factors. The all important consideration was the quality of the collapse, particularly whether all cavities were closed and the collapse well maintained. Women in whom this was true came through pregnancy without harm and were able to lead normal lives the same as any nontuberculous mother.

Stabilized tuberculosis not controlled with collapse therapy presented an entirely different problem. Fibrous strands, or thickened pleura with or without salients into the lung structure, or calcified spots were of no clinical importance. Such patients did well.

When the tuberculosis, however, extended beyond these limits and was not controlled with pneumothorax, serious relapses followed in some instances. This was true regardless of how long or how well stabilized the tuberculosis appeared to be or how minimal in extent at the time of pregnancy. In retrospect, there is no certain way of determining beforehand which tuberculous patient will do well and which one will not, during and following pregnancy except through trial and error; consequently, each succeeding pregnancy is a new problem. Some relatively inactive and apparently healed cases tend to break down under the stress of pregnancy so that the disease may become worse rapidly and endanger the life of the mother. Again, the mother may go through one pregnancy without harm, but break down during another without apparent reason. The risk to the tuberculous mother, therefore, of pregnancy reactivating an apparently inactive tuberculous lesion not controlled with collapse therapy is real and must be taken into consideration in advising pregnancy. Reactivation of mild inactive tuberculosis not treated with pneumothorax may be expected in approximately 30

per cent of cases, and in about half of this number, collapse therapy may actually be necessary to bring the reactivated tuberculosis under control. Obviously, the more extensive the disease and the less stabilized, the greater the risk. In this respect, it is worth recalling that Norris and Landis<sup>1</sup> in a study of 103 pregnant women made at the Phipps Institute and the University of Pennsylvania Hospital in 1918, in the days when little or no collapse therapy was used and routine x-ray studies of the chest were uncommon, found that about 20 per cent of mild, quiescent cases and 70 per cent of more advanced cases exhibited exacerbations during pregnancy or the puerperium.

### Summary and Conclusions

This presentation concerns itself with the immediate and late effects of pregnancy, and the responsibilities which follow, upon advanced tuberculosis in a single series of twenty-six white women who were treated with collapse therapy to control the tuberculosis before giving birth to one or more children. These women were of about the same social and economic status and have been under constant clinical and roentgenologic observation for varying periods during the past fifteen years. The average for the group was approximately nine years.

These twenty-six women had forty-eight known pregnancies following collapse therapy and gave birth to forty children, of whom thirty-six are alive and well. Fifteen women gave birth to one child, nine to two children, one to three children (one set of twins), and one to four children.

While the number of cases reported is too small to warrant definite and final conclusions, this study does point to certain facts:

1. Pregnancy, and the responsibilities which follow, can and do affect some patients with tuberculosis unfavorably; therefore, childbearing should be looked upon as a potential hazard for a tuberculous mother. Exacerbation may occur either in the early months of pregnancy or within the first few months following delivery.

2. Collapse therapy has definitely minimized this risk and has brought a better outlook to the expectant tuberculous mother. It has restored to her the right of motherhood. Each case, however, must be carefully evaluated on its own merits, including physiologic and social factors, as well as pathologic, before deciding for or against pregnancy.

3. If the disease, though advanced, is limited to one lung, as indicated by x-ray, and the diseased area is anatomically well collapsed with all cavities closed, the sputum free of tubercle bacilli, and the collapse maintained throughout pregnancy, there is little or no risk of reactivating the tuberculosis and such women may safely undertake one or more pregnancies. The same is true if there is advanced tuberculosis in both lungs, but with the disease in each lung controlled with adequate collapse therapy. Indeed, one may regard the interval of effective collapse therapy as the safest period for a tuberculous woman to marry, have children, and rear a family.

4. If there is disease in both lungs and only one lung, the "worse" lung, is treated with localized collapse therapy, the disease in the uncollapsed lung, although quiescent before pregnancy, may become active in approximately 30 per cent of cases. In about half of this number, collapse therapy may actually be essential to control the reactivated disease in the untreated or contralateral lung. This is true even if the disease in the contralateral lung is minimal in extent, well stabilized for months or years, and the sputum negative for tubercle bacilli at the time of pregnancy. The risk, of course, is greater when the disease is more advanced and less stabilized.

5. The possibility of reactivating quiescent tuberculosis in an uncollapsed lung, however, is not in itself a contraindication to pregnancy. Permission may be given as long as the patient is kept under observation and is willing to accept collapse therapy when it first becomes indicated. Such women may assume the added hazard of pregnancy to their tuberculosis with the assurance that effective help is available when needed.

6. Pneumothorax therapy may be considered as an alternative to therapeutic abortion in the presence of active tuberculosis first recognized during the early months of pregnancy. When the collapse is good and promptly controls the tuberculosis, the woman may proceed safely to term.

7. Only collapse therapy which produces adequate localized collapse of the diseased portion of the lung, such as pneumothorax, maintenance oleothorax, or thoracoplasty, will prevent reactivation of the disease. Indirect collapse, such as phrenic nerve interruption, is not enough.

8. Inadequate collapse therapy—that is, inability to close cavities and render positive sputum free of tubercle bacilli—may be considered the same as if no collapse therapy is employed so far as the effect of pregnancy on the tuberculosis is concerned. The majority of such patients with advanced disease do poorly and pregnancy is inadvisable.

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## THE CONSTITUTIONAL TYPE OF FEMALE PRECOCIOUS PUBERTY WITH A REPORT OF 9 CASES

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**P**RECOCIOUS puberty is generally looked upon as due to an endocrinopathy of one sort or another, and most often to a tumor of one of the ductless glands. When it occurs in the female suspicion is likely to turn first to the ovary, because of the fact that granulosa cell tumors of this organ have been shown to be capable of producing the syndrome of premature puberty when they arise in early life. There can be no criticism of alertness to this possibility, but it should be borne in mind that, while granulosa cell tumors are no longer looked upon as rare, they are certainly far more infrequent in young children than they are during and after reproductive life. As a matter of fact, in the most recent review of the subject (1941) Lull<sup>1</sup> was able to collect from the literature only 16 cases in which granulosa cell tumors had been found responsible for premature puberty.

One of the purposes of this paper, as a matter of fact, is to emphasize that this granulosa cell tumor type of sex precocity is really much less frequent than certain others. Emphasis on this point is not purely academic. In the days of our early lively interest in the then newly recognized granulosa cell type of tumor, some of us, including myself, were wont to assume the probable existence of such growths when confronted with cases of female sex precocity, even when no tumor could be clearly demonstrated by palpation. Knowing that even small endocrine growths can produce profound biological effects, exploratory laparotomy has often been done in the hope of revealing small neoplasms in the ovary. In the majority of such cases no tumor will be found, and, to anticipate, one of the conclusions of this paper will be that if careful pelvic examination under anesthesia reveals no suggestion of ovarian enlargement or tumor, there is no indication for exploratory operation. I shall, however, return to this point later.

### Causes of Female Precocious Puberty

As regards sex precocity in general, the endocrine tumors which may be responsible have been considered to be those of the adrenal, the pineal body and the gonads. It is curious that, in spite of the dominating role of the pituitary in the endocrine mechanism of reproduction, there is no reported instance of a pituitary tumor in association with precocious puberty.

### Adrenal Tumors

There is ample evidence that tumors of the adrenal body can produce precocious puberty in either sex, more often in females than in males. This variety, however, will rarely be encountered in gynecologic practice. Its clinical features are such that it will not often be confused with the syndrome evoked by granulosa cell tumors. Precocious menstruation, for example, is an unusual feature, having been observed in only 4 of the 40 cases of adrenal type collected by Reilly, Lissner and Hinman.<sup>2</sup> The premature developmental changes are of dominantly heterosexual character, with hirsutism, hypertrophy of the clitoris and in some cases the pronounced muscular development which brings about the so-called "infant Hercules" appearance. In a minority of cases obesity may be a pronounced feature of the syndrome. The degree of heterosexual development depends upon the age at which the cortical lesion develops. In the congenital or fetal group, actual pseudohermaphroditism may be produced. When the lesion develops in early childhood, with which phase we are more particularly concerned in this paper, the syndrome of macrogenitosomia results, characterized by the symptoms already mentioned. In adults varying degrees of the so-called virilismus are brought about.

On the whole, the effects of such lesions are masculinizing or virilizing, in contrast to the purely feminizing or prefeminizing effects of granulosa or thecal tumors of the ovary. This distinction is well shown in the hypertrichosis which is a part of both syndromes. With ovarian feminizing tumors the hair growth is seen only on the genitalia and in the axillae, where it occurs normally at puberty. With adrenal macrogenitosomia, on the other hand, it involves also other parts of the body, such as the face, back, abdomen and extremities.

### Pineal Tumors

The role of pineal tumors, especially teratomata, in the production of premature sex development, appears to be attested by the report of a considerable group of cases of such an association. Bing, Globus and Simon<sup>3</sup> were able in 1938 to collect from the literature 177 such cases. The fact that only 1 of these was in a female justifies the statement that this variety is of little practical significance in gynecologic practice. Furthermore, the syndrome produced by such lesions, macrogenitosomia pinealis, is apparently quite similar to the macrogenitosomia of adrenal cortical tumors. Finally, evidence is accumulating to the effect that the sex manifestations of pineal tumors are merely the results of pressure upon certain brain areas in the floor of the third ventricle or hypothalamus, and not to any endocrine effect emanating from the pineal body itself.

### Ovarian Tumors

As to the role of ovarian tumors, those of granulosa and thecal type, there is of course no doubt that these, when they arise in early life, do bring about precocious puberty, and a true puberty in the sense that, with one important exception, the phenomena produced are like those normally seen at puberty. The exception to which I refer is that ovulation is lacking, the menstrual periods being of the anovulatory, estrogen-induced type. This is in sharp contrast to the "constitutional" group of cases with which this paper is chiefly concerned, as I shall later emphasize.

I have already referred to the rarity with which ovarian tumors are found to be responsible for premature puberty. Only one case has been encountered in the department of gynecology among the more than 60,000 patients who have been treated in the past 60 years. This case I reported in 1933,<sup>4</sup> together with two others from which tissue had been sent to our laboratory for study from other institutions. At that time there had been reported only 3 other instances of this type, and in all the years since then the total number in the literature of the world has risen to only sixteen.<sup>1</sup> I mention this to emphasize again that, interesting and important as this type of precocious puberty is, I believe it to be much less common than the non-neoplastic variety which will be presently described.

### Cerebral Type

A considerable number of cases have been described in which precocious puberty has been produced by lesions involving various portions of the brain, and especially the region of the hypothalamus and the floor of the third ventricle. It has already been mentioned that pineal tumors probably bring about precocious sex changes through pressure effects upon the above-mentioned brain areas, and it is quite possible that a similar mediation explains sex precocity produced by encephalitis, tumors of the tuber cinereum and mammillary bodies, hydrocephalus and various other brain lesions which have apparently brought about precocious sex phenomena. Even the case reported by Ford and Guild,<sup>5</sup> of precocious phenomena due to postmeasles encephalomyelitis, may be explained by some such mechanism.

As for actual tumors of the hypothalamus, Weinberger and Grant<sup>6</sup> have collected 15 cases in which such growths, with no involvement of the pineal, had brought about precocious sex development. On the other hand, many cases of pineal tumor have been noted in which no sex changes had been observed. These authors have brought together a considerable array of both clinical and experimental evidence concerning the functional interrelationship of the hypothalamus and the hypophysis. There is as yet no certainty as to the exact mechanisms involved, but the concept of Bing, Globus and Simon<sup>3</sup> has the ring of plausibility. These authors believe that, while the pituitary dysfunction is directly responsible for the sex phenomena, it in turn is caused by disturbances in the innervation from the hypothalamic areas as a result of lesions involving that region.

Finally, it is probably in this cerebral group that we can, tentatively at least, place the so-called Albright syndrome, described first by Albright, Butler, Hampton and Smith in 1937.<sup>7</sup> This may occur in either males or females, but apparently only in the latter is premature sex precocity observed. However, the sex changes are overshadowed by the other phenomena of the syndrome, which consist of widespread skeletal changes in the form of osteitis fibrosa disseminata and often bone cysts, together with cutaneous pigmentation. While instances of Albright's syndrome are being reported with increasing frequency, it will scarcely be encountered in gynecologic practice, and it is mentioned here merely for the sake of completeness.

### Constitutional Type of Precocious Puberty

There is one other type of precocious puberty which I believe to be the most common of all, but it has received the least attention in the literature. This is probably due to the fact that it occurs in the absence of any tangible or demonstrable cause, while with the others a definite etiologic factor, such as a tumor of one of the endocrine glands, can be discussed as the probable or undoubted cause of the syndrome. In cases of what may be called the constitutional group, however, no such factor is demonstrable, nor does the subsequent course of the patient suggest that such a factor may have existed and been overlooked. Patients of this group simply develop perfectly normal puberal phenomena at an abnormally early age, appearing to skip all or part of their childhood, and at times jumping from infancy to puberty.

The classical work of Smith and Engle, paralleling that of Zondek and Aschheim, has established beyond doubt that the motivation of puberal functional activity in the ovaries is evoked by the underlying gonadotropic activity of the anterior pituitary. This would at once suggest that in these cases of precocious puberty in which no lesion of any other endocrine gland ever materializes there might be present in the anterior pituitary an adenoma, perhaps of very small, subclinical size, and that this might bring about the syndrome, much as a tiny basophilic adenoma can produce the profound biological changes characterizing the Cushing syndrome. However, it is a remarkable fact, as already mentioned, that in not a single reported case of precocious puberty has a tumor of the pituitary been demonstrated. On the other hand, tumors of glands which may be considered to be of only auxiliary sex importance as compared to the pituitary, have been frequently reported.

What, after all, is the biological significance of normal puberty? The easy explanation which we so complacently set forth is that the responsible factor is the ovarian estrogenic activity which begins at a certain age, producing characteristic physiological and anatomical changes in certain tissues and organs. Two factors are thus essential to the production of the puberal phenomena, viz., the ovarian hormone and the selective responsiveness of certain body tissues and organs. But why do these factors so inexorably go into conjunction at a characteristic age of  $13\frac{1}{2}$  or 14 years, with usually only minor individual variations in either direction? Certainly this is not to be explained by absence of sensitivity in the recipient organs and tissues before this age, for even in the infant and very immature girl estrogen stimulation can bring about puberal changes, as is well illustrated by the effects of granulosa cell tumors at this age.

And how are we to explain the selective effect of these hormones upon certain tissues, often far removed from one another, such as the genitalia, the breast, the axillae and the larynx, except on the basis



of an underlying foreordained sex pattern innate in the human mechanism, and having its source in the chromosomes themselves? To try to explain all of the normal sex phenomena or their many abnormalities on a purely endocrine basis is superficial and wrong. While the immediate motivating force in the reproductive physiology is the endocrine system, primarily the ovaries and the hypophysis, there is no evidence that it plays an important part in certain more fundamental aspects of sex differentiation. We know very little as yet as to how these two forces interdigitate and how they supplement each other.

No other explanation seems possible than that the underlying factor which normally brings about the characteristic development of puberal changes at a certain age period emanates from certain genes, though we know almost nothing as to the mechanism involved. Puberty may be advanced or it may be retarded by endocrinopathies of one sort or another. On the other hand, it may be advanced or retarded also as a result of an abnormal genic factor. In the case of precocious puberty, therefore, such a genic abnormality may set the characteristic female endocrine mechanism into motion at an abnormally early age. This concept would seem no less rational than the commonly accepted explanation of hemophilia as due to an abnormal gene of recessive type in the sex chromosome. Bauer<sup>8</sup> has developed very elaborately this thesis of the probable constitutional or genic nature of various diseases, including some which parade clinically as endocrinopathies, and are commonly so considered and treated.

Whether or not this concept is correct, certainly there is no evidence in the cases of precocious puberty which are discussed in this paper of any purely endocrine factor, neoplastic or otherwise, nor do they come into any of the other categories which have been enumerated. They are all characterized by the development in otherwise normal children of puberal changes which are entirely normal except for the age at which they appear, and their later course reveals no other abnormality. Such patients simply skip from infancy or early childhood to puberty. In so far as our present knowledge is concerned, the designation of constitutional appears to be justified for this type of precocious puberty.

### **Incidence of Constitutional Type**

As to the incidence of the constitutional type of sex precocity I do not believe that any intelligent estimate can be derived from a study of the literature. Not only must many cases go unrecorded, but others have been reported simply as instances of precocious puberty of obscure or uncertain causation, or have been buried in the reports of series of cases of all sorts of etiological types. This is true of even such exhaustive reports as those of Reuben and Manning,<sup>11</sup> Neurath<sup>9</sup> and Lenz.<sup>10</sup> For example, in the collective review of 130 cases made by Lenz in 1913, it is quite clear that in addition to his own patient,

several others in his series are of constitutional type. The case of Robbelin, in which menstruation appeared at 6½ years, was followed for 26 years, during which time she remained well and menstruated normally. Such a history would appear to exclude neoplastic disease, especially as most of the reported cases of adrenal, pineal or hypothalamic type have succumbed within a comparatively short time. Lenz's own patient, in whom menstruation began at four, was observed until the age of 14, when she was still entirely well and menstruating normally. One of my own cases (Case 1) was observed from the age of 16 months to 10 years, during which she remained well except for her regular menstruation and other puberal characteristics. A review of many other cases reported in the literature as of obscure causation leads me to the conclusion that they belonged to this group (Elterich,<sup>12</sup> Fischer,<sup>13</sup> Craven,<sup>14</sup> Mengert,<sup>15</sup> etc.). For reasons which I shall elaborate later it seems certain that in this category we must also place the remarkable cases of abnormally early pregnancy which have been reported from time to time.

If my own experience with this variety of precocious puberty could be taken as an index of its comparative incidence (I appreciate the fact that it cannot) it would seem far more frequent than the only other variety with which it is likely to be confused, or which is apt to be encountered by the gynecologist, i.e., the granulosa cell ovarian tumor group. While I have reported 3 cases of the latter group, none has occurred in my own practice, and only 1 of the three was encountered in the gynecologic department of the Johns Hopkins Hospital. On the other hand, I am reporting today 9 cases of the constitutional type, and 6 of these were observed in my own private practice. Two of the remaining cases were encountered in the Harriet Lane Home for Children of the Johns Hopkins Hospital, and for permission to add these to my own I am indebted to Dr. Edwards A. Park, the director of the Harriet Lane Home. One case was from the practice of Dr. Thomas K. Galvin, who kindly sent me sections of the ovarian biopsy and permitted me to include the case in this series.

### Clinical Characteristics of Constitutional Variety

According to most authors puberty should be considered abnormally early or precocious when it occurs below the age of 9, although some suggest a lower limit of 8. I need not here elaborate on the obvious distinction between puberty and the menarche, or stress the fact that the first menstruation is only one of the developmental phenomena which characterize puberty. It is only natural, however, that the first menstruation, constituting as it does the most conspicuous phenomenon of puberty, has in the literature been utilized as the most convenient chronological marker for the puberal epoch. I may add that the ages of the 9 patients reported in this paper were well below even the arbitrarily set minimum of 8 years. A number of additional cases in

which the age was within a year or so of this limit has been excluded from the report. The age at which the first menstruation occurred in the 9 patients of my series was as follows: 15 months, 2; 2 years 8 months, 4;  $4\frac{1}{2}$ ,  $6\frac{1}{2}$ , 7 (2 cases),  $7\frac{1}{2}$ .

Not much need be said about the clinical characteristics of this type of precocious puberty, as they are apparently exactly those seen with normal puberty except for the age at which they appear. These precocious children are apt at first to be taller than normal for their age, but their later growth is likely to be inhibited and they might then be shorter than the average. Lenz's patient, for example, was for some years taller than her 2 year older sister, but at 14, the latter had outstripped her in height. For a full discussion of the skeletal growth changes in cases of precocious puberty the reader may be referred to Lenz's paper.<sup>10</sup>

There are, so far as I know, practically no available data as to the age at which the menopause occurs in these patients, although it seems likely that the climacteric epoch is not notably accelerated. This would seem to be indicated by the fact that Robbeline's case<sup>10</sup> was still menstruating normally at  $32\frac{1}{2}$  years, and that Haller's patient,<sup>10</sup> in whom menstruation appeared at  $2\frac{1}{2}$  years, had her menopause at 52. So far as I can find there is available in the literature no report of autopsy in any patient who had passed through this form of sex precocity, and it is probable that the post-mortem study of the endocrine glands would not be especially revealing.

The clinical feature of these cases which distinguishes them from the granulosa cell group, and which has apparently received no previous emphasis, is that *in the constitutional group the patients not only menstruate unusually early, but they also ovulate*. By contrast, the granulosa cell patients menstruate but they do not ovulate. The periodic bleeding in the latter group is, in other words, of the purely estrogen-induced type. In the constitutional group, on the other hand, the full puberal mechanism is evoked, with both menstruation and ovulation. That this is so is indicated by the fact that in 3 of my cases in which exploratory operation was done biopsy of the ovaries revealed indubitable evidence of preceding ovulation in the form of corpora lutea at various phases (Cases 1, 2 and 4).

The practical significance of this observation is that in certain cases of the constitutional variety pregnancy is possible if insemination occurs, while this is not true of the granulosa cell tumor group. As a matter of fact, it seems certain that all of the cases of abnormally early pregnancy which have been reported must have been cases of the constitutional puberal variety, in which both menstruation and ovulation had been evoked at abnormally early ages. The recent much publicized case of Lina Medina, the Peruvian child who gave birth to

a child at the age of 5 years and 8 months, making her the youngest mother in the world's history, undoubtedly belongs to this category. According to Escomel's report of this case,<sup>16</sup> menstruation had begun at 7½ months and continued until impregnation. At the time of her cesarean section biopsies of the ovary were made, showing an adult type of ovarian tissue and also the corpus luteum of pregnancy. The much quoted case of Anna Mummenthaler, reported in 1751 by Haller,<sup>17</sup> concerned a patient in whom menstruation appeared at 2, with the first childbirth at 9. Another well-known case, also in the very old literature, is that of Mandeslo,<sup>18</sup> in whom a child was born to a girl of 6, in whom menstruation had occurred at 3. In the case of precocious puberty reported by Chaschinsky and Jershow in 1933,<sup>17</sup> full-term pregnancy occurred at the age of six. A goodly group of other cases of abnormally early pregnancy have been reported, and no explanation seems possible except that they represented instances of constitutional precocious puberty.

As with normal puberty, ovulation is not necessarily inaugurated when menstruation begins. It is highly probable that in children exhibiting this form of precocious puberty the early cycles are not infrequently anovulatory, and this would seem to be at least suggested by the operative and biopsy findings in one of my cases (Case 9). Data on this point are too meager to justify any generalizations. Moreover, as with normal puberty, the rhythm of menstruation is not necessarily regular in these precocious cases, and periods of amenorrhea may be noted, as in my Case 5.

### Management

There are two points of obvious importance in the management of these patients which deserve emphasis. The first pertains to the psychological management of the patient and her family, especially the mother. The latter is quite sure to be distressed by the abnormally early appearance of menstruation and other sex manifestations in the child. The situation should be explained to her as fully and fairly as possible, with reassurance as to the essential harmlessness of the condition in itself. She should be told that the precocious manifestations will persist, but that after the age of about 9 or 10 the child will not be different from many other girls of her age. It is inevitable that in the earlier years of childhood the sexually precocious girl will be conscious of the differences between herself and others of her age, and one can understand the self-consciousness and morbidity which this is likely to engender. An understanding and sympathetic mother can render her child a great service by her guidance and protection through these trying years.

The second point to stress is that since ovulation may undoubtedly occur in girls with this type of precocious puberty, they must be care-

fully guarded against sex violations, which might result in impregnations. One naturally hesitates to question children on the subject of possible sex attractions, but in at least one of my cases the mother volunteered the information that the child was "very fond of the boys." It is easy to understand that the reverse might also be true, in view of the physical attractiveness of some of these young patients.



Fig. 1.—Case 1. Age 16 months. First menstruation at 15 months. Patient entirely well and menstruating normally at age of 10 years.

### Case Reports

*Case 1.*—R. R., aged 15 months, was first seen at the Harriet Lane Home, Johns Hopkins Hospital, in April, 1932, in consultation with Dr. Edwards A. Park, who later kindly referred her to me for further management. When the child was 6 months old, the mother noticed a white vaginal discharge, which recurred again one month later, and again three months thereafter. At this time enlargement of the breasts was first noted. After this the vaginal discharge persisted, but repeated examinations revealed no evidence of gonococcal infection. There was no further medical examination until the child, at 15 months, was brought to the Johns Hopkins Hospital for treatment. At this time there was a fairly profuse whitish discharge, which on smear showed many large epithelial cells and no pus cells. Bacteriologic examination showed only a mixed flora of gram-positive organisms. A few days later the child had a profuse menstrual bleeding lasting 2 days, with staining for 2 additional days. She was then admitted for further study.

The child (Fig. 1) was then a rather pretty, intelligent Jewish girl of 15 months, slightly taller than the average for her age, her height being 85 cm. and weight 9,850 Gm. Both breasts were moderately enlarged. The genitalia showed a moderate growth of dark hair, and there was a similar growth in the axillae. Both the labia majora and minora were well developed, and the uterus, on rectal examination, was almost 5 cm. in length. Both ovaries were definitely larger than those of a normal child, the right being distinctly larger than the left. Hormone examinations of the urine were made by Dr. R. T. Frank, who reported approximately 40 mouse units of estrogen with small amounts of gonadotropic hormone. X-ray study showed bone development to correspond to her age, with a normal sella turcica. Numerous other studies, including a ventriculogram, were made with essentially negative results. The child was then discharged and referred to me by Dr. Park for further management.

When seen again on November 17, 1932, the puberal changes had become more fully developed. Her height had increased to  $38\frac{1}{4}$  inches (97 cm.) and she weighed 25 pounds. Menstruation had continued to recur at approximately monthly intervals, and the pelvic examination showed the right ovary still distinctly larger than the left, so that the possibility of a small granulosa cell tumor could not be eliminated, and the child was admitted to my service at Bon Secours Hospital for exploratory operation.

The laparotomy showed the pelvic organs to be of essentially normal puberal appearance. The uterus was  $5\frac{1}{2}$  cm. in length, with a full and rounded fundus. The left ovary measured 2 by 1 by 1 cm. but the right was considerably larger, measuring  $2\frac{1}{2}$  by  $1\frac{1}{2}$  by  $1\frac{1}{2}$  cm. with slight lobulation apparently due to the presence of cystic follicles beneath the surface. One surface follicle measured 1 cm. in diameter. No neoplasm could be felt in either ovary, and an incision into the right ovary disclosed none. A yellowish body, evidently a retrogressed corpus luteum, was encountered just beneath the surface and a biopsy was made in this area (Fig. 2). The microscopic examination confirmed the nature of the retrogressed corpus luteum. The adrenals were normal in size.

Since this operation the patient has returned to Baltimore for examination on a number of occasions. She has been entirely well and has

been menstruating normally and without pain. No sign of any granulosa or other endocrine tumor has ever developed. The last examination was made 2 years ago, after which her mother moved to another city, and it has not been possible to trace her.

*Case 2.*—E. M., aged 9, was referred to me on April 28th, 1938, by Dr. James Taylor, of Altoona, Pa. At the age of 6 the breasts began to grow large and full, with rounding of the figure and the appearance of axillary and pubic hair. Her general appearance, when first seen, was that of a girl of about 13 or 14 (Fig. 3). Her height was 54 $\frac{1}{4}$  inches, and her weight 90 pounds. She was bright and vivacious, and her school work was described by her mother as of average grade. The first menstruation occurred at 7 $\frac{1}{2}$  years, with intervals for a time of 28 days, but more recently 19 or 20 days, the amount being quite profuse.

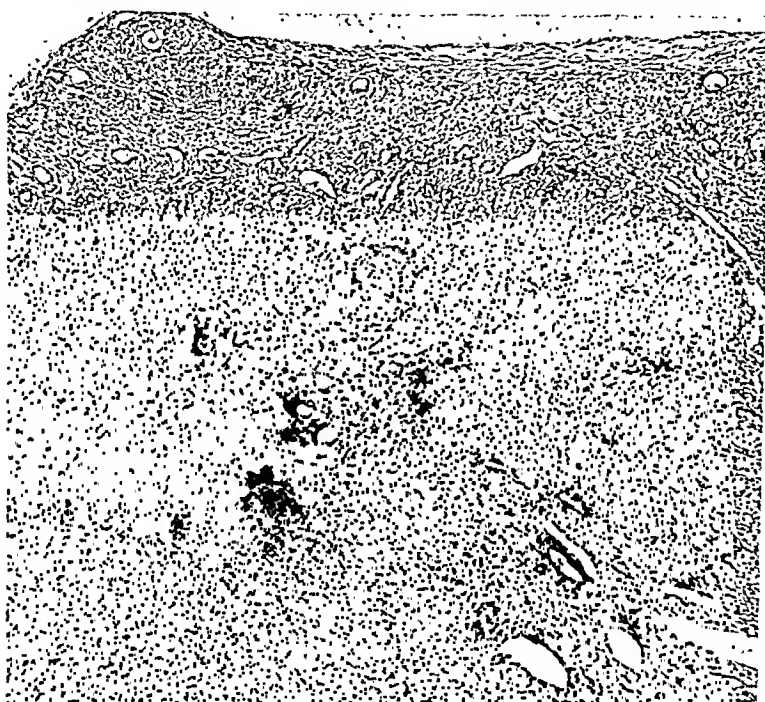


Fig. 2.—Typical corpus luteum in slightly retrogressive phase in ovary of Case 1.

The genital findings need not be described in detail, since they were those characteristic of the normal girl of puberal age. The left ovary was enlarged to about the size of a walnut, so that a small granulosa growth could not be excluded. Routine laboratory studies yielded normal findings. Estrogen determinations by Dr. Brack showed a hormone content only slightly lower than that of the average puberal girl. X-ray studies showed epiphyseal closure not yet complete, and the sella was normal. Neurologic studies were negative. Because of the enlargement of the left ovary, and the possibility of a small granulosa tumor, an exploratory laparotomy was thought advisable.

Operation revealed pelvic organs of puberal degree of development. The slight enlargement of the left ovary was due to a small follicle cyst. A yellowish body was noted just beneath the surface of the left ovary, and a biopsy at this point confirmed the presence of the corpus luteum shown in Fig. 4.



Fig. 3.—Case 2. Age 9 years, but menstruating normally since age of  $7\frac{1}{2}$ .



An examination of this child 1 year after operation showed no suggestion of ovarian neoplasm, and a very recent report from the mother states that she is quite well, with normal menstruation.

*Case 3.*—S. H., aged 9 years, was referred to me on February 27th, 1938, by Dr. E. W. Johnson of Baltimore. Since the age of 6½ she had menstruated at about 4 weekly intervals, the flow lasting 5 days, moderately free, with no pain. At approximately the time of the menarche the breasts began to enlarge and hair appeared in the axillae and on the genitals. The breasts since then have become quite large, and she now has the appearance of a girl of 14 or 15 (Fig. 5). The pelvic examination showed the uterus to be of normal puberal size, and the ovaries were likewise much larger than that of a normal child of her age, the left



Fig. 4.—Corpus luteum from ovary of Case 2.

being larger than the right. The urinary hormone study, made by Dr. C. B. Brack, showed an output of more than 3.3 and less than 4.4 R. U. per liter. Other laboratory studies were negative, and will not be detailed. Because of the left ovarian enlargement exploratory laparotomy was done, but it showed no granulosa tumor. The ovarian enlargement was due to the presence of a small follicle cyst. There was no gross evidence of corpora lutea. A biopsy of the left ovary was done, showing follicles in various stages of maturation, but no evidence of corpora lutea, though the examination of one small bit of ovarian tissue could not of course exclude the presence of lutein tissue elsewhere.

*Case 4.*—L. F., aged 10, was referred to me by Dr. Gabriel Pickar, of New Brunswick, N. J., on January 17th, 1941. She had begun to menstruate at the age of 4, and at about the same time the breasts exhibited marked hypertrophy, with soon an abundant growth of axillary

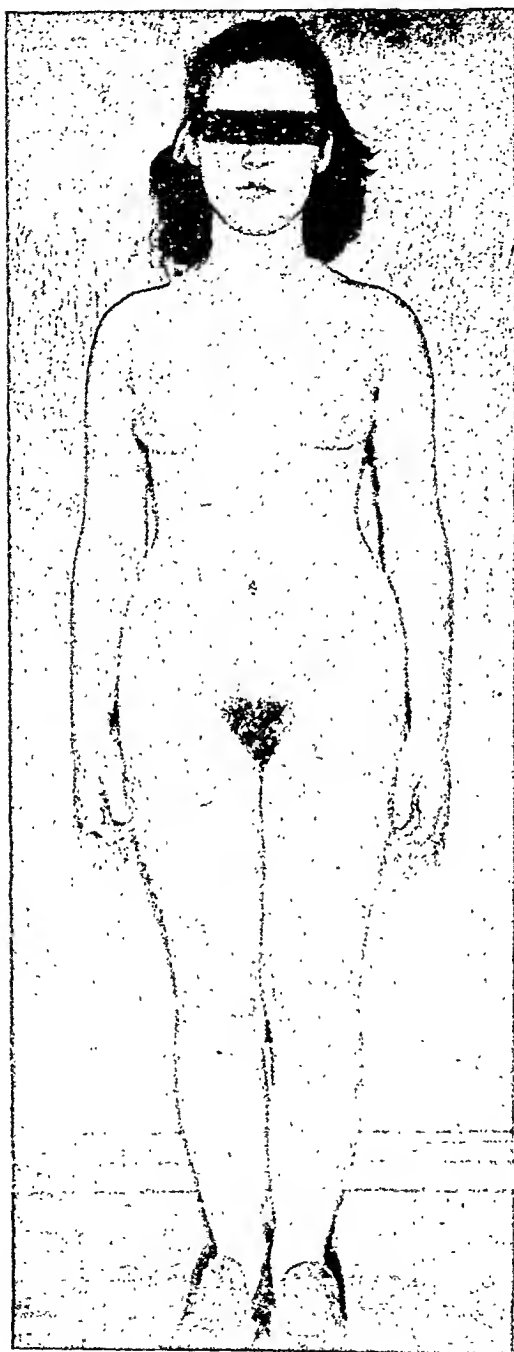


Fig. 5.—Case 3. Age 9 years, but menstruating regularly since the age of  $6\frac{1}{2}$ .



Fig. 6.—Case 4. Age 10 years, but menstruating normally since age of 4.

and genital hair. The periods have since then occurred at regular intervals of about 4 weeks, and the figure has become full and rounded. (Fig. 6.) She is of normal intelligence for her age, and is described by her mother as rather "fond" of the boys. At the age of 5 the patient was operated upon at a hospital in Trenton with a preoperative diagnosis of granulosa cell tumor, and the left tube and ovary were removed. There was, however, no recession of the precocious sex changes. An effort was made to secure tissue or slides, but this was unsuccessful. Some time later, however, Dr. Piekar was able to ascertain that the pathologist's report indicated no evidence of tumor, the sections showing what he interpreted as normal adult ovarian tissue.

Following the operation the patient developed considerable pain in the left lower quadrant, and as there was still a clinical suspicion of granulosa tumor, the patient was referred to me for treatment. She was then 10 years of age.

Her general appearance, as will be seen from her photograph (Fig. 6), was that of a girl of perhaps 14 or 15 and, without going into detail, the generative organs likewise corresponded to that age. Her height was  $55\frac{3}{4}$  inches, and her weight 105 pounds. Routine laboratory studies showed normal findings, as did the neurologic examination. X-ray studies of the bones showed the epiphyses already closed. The sella was normal. Basal metabolic rate was minus 21 per cent. Estrogen urinary studies by Dr. Georgeanna Seegar-Jones showed an output of between 20 and 25 rat units.

The pelvic examination made per rectum showed the uterus to be of about the average nulliparous adult size. The right ovary likewise was well developed. There was extreme tenderness in the left side, with some thickening, but no evidence of a tumor of any sort. Because of the patient's constant pain in this region, laparotomy was considered to be advisable.

The operation showed the uterus and right adnexa to be of adult type. The surface of the ovary revealed considerable pitting, indicative of previous ovulations. One or two small cystic follicles were seen on the surface, and also a yellowish body which was evidently a retrogressed corpus luteum. A biopsy was done at this point, and the sections show typical retrogressive lutein cells. (Fig. 7.) The left adnexa had been removed. There were rather extensive and firm adhesions involving the left broad ligament, omentum and several loops of small intestine. These were freely mobilized, with satisfactory peritonealization. Exploration of the abdomen, including the adrenals, showed no sign of any tumor masses. The postoperative course was smooth, and the patient has been free of pain. She has of course continued to menstruate.

*Case 5.*—B. H., aged 2 years and 8 months, was referred to me on May 17, 1941, by Dr. Robert L. McCrady of Charleston, S. C. She weighed 7 pounds 11 ounces at birth, and had been normal until January, 1941, when her breasts began to enlarge. (Fig. 8.) Several months later a growth of axillary and genital hair appeared, and 10 days previous to my examination, the first menstruation occurred, lasting 2 days. She weighed  $33\frac{1}{2}$  pounds and was  $36\frac{1}{4}$  inches in height. A pelvic examination made under anesthesia showed the uterus to be of approximately puberal size, measuring 5 cm. in length. The left ovary was small and beady, the right somewhat larger, but smooth and ovoid.

There was no suggestion of tumor. Other laboratory studies were negative, and the child was discharged, with instructions as to the psychologic management, and as to the importance of periodic examinations.

A letter from her mother on June 17, 1942, reports that menstrual bleeding occurred June 5, June 21, and again July 4, followed by a long period of amenorrhea, with later re-establishment of the flow. Her health otherwise has been excellent.



Fig. 7.—Corpus luteum revealed by ovarian biopsy in Case 4.

*Case 6.*—A. W., aged 6, of Emmitsburg, Md., was seen at Bon Secours Hospital on August 12, 1940. She had entered the hospital for tonsillectomy 2 months previously, and at that time the physical examination showed marked breast development, though she had not menstruated. As her parents, who lived in Emmitsburg, Md., could not then leave her for further study, they were requested to do this later, and she returned in August. At this time she was seen to be tall for her age, her height being 52½ inches. She weighed 63 pounds. The breasts showed striking development. (Fig. 9.) There was only a light beginning growth of axillary and pubic hair. The pelvic examination, without going into details, showed a subpuberal stage of development, with fairly well-developed labia, a uterus which measured approximately 5 cm. in length, and ovaries definitely larger than those of a normal child of 6. There was no palpable suggestion of any ovarian neoplasm. Laboratory studies were essentially negative.

Although the patient had not yet menstruated, it seemed reasonably certain that she would before very long, and this prediction was made and the mother told of the probability. A letter received from her later reported that the first period occurred in April, 1941, eight months after she was seen, at the age of 7. She states that the child has been perfectly well, except for some of the infectious diseases

of childhood, and that she is "extremely bright in her school work and in her music, and she has a wonderful memory."

*Case 7.*—S. F., aged 7, was admitted to the Harriet Lane Home for Invalid Children on Dec. 20, 1914, because of unusual breast development. (Fig. 10.) Her birth weight was 8 pounds. She was 52½ inches tall, and weighed 68 lbs. The breasts began to develop at the age of 4, becoming quite large in succeeding months. At the time of admission they were described as 16 cm. in diameter, pendulous, with well-marked areolae about the nipples. There was an abundant growth of pubic hair, but none in the axillae. At this time she had not begun to menstruate. Neurologic, x-ray studies and other laboratory studies were essentially negative. The external genitalia were described as much more developed than those of a girl of her age, but unfortunately there is no note as to gynecologic examination.



Fig. 8.—Case 5. Age 2 years and 8 months at this time. First menstruation 10 days before this picture was taken.

She remained in the hospital only a few days, but returned to the dispensary on Dec. 31, 1914, when her mother reported that the child had had a bloody vaginal discharge, evidently menstrual. Shortly after this the family moved to parts unknown, so that the efforts of the social service department to get her back for further study were unsuccessful.

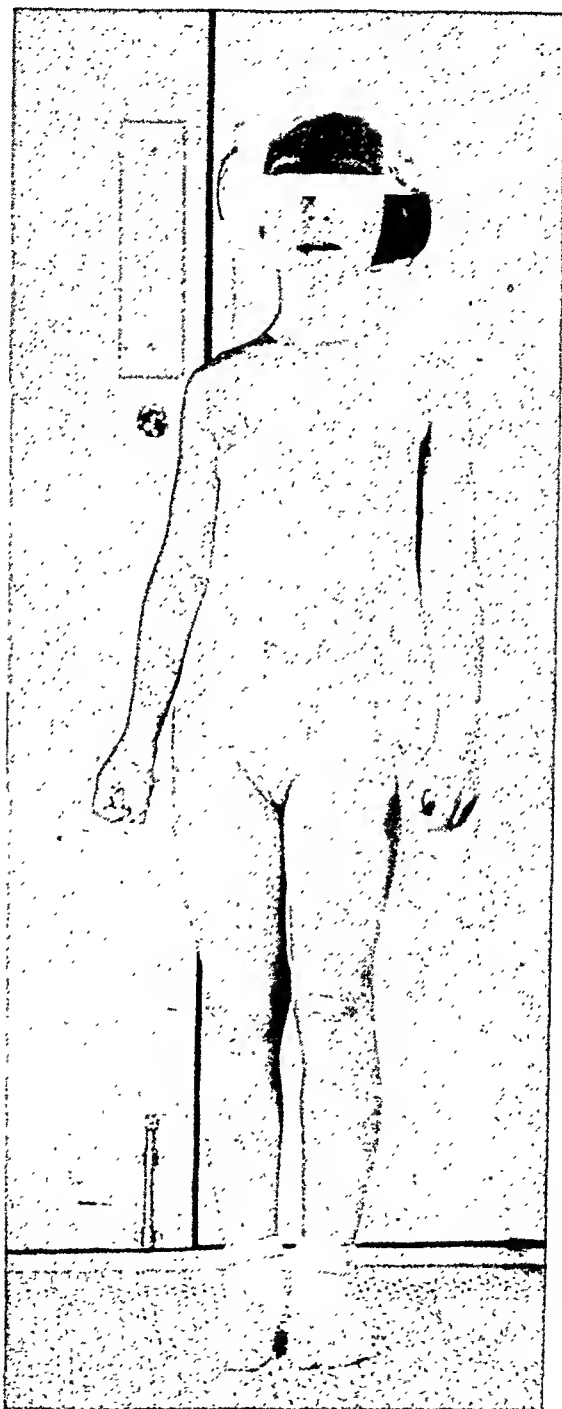


Fig. 9.—Case 6. Age 6 years at this time. Beginning puberal development but no menstruation. Eight months later first period occurred and menstruation has been normal since then.

*Case 8.*—L. McD., aged 6½, was admitted to the Harriet Lane Home for Invalid Children, Johns Hopkins Hospital, on April 6, 1939. At the age of 2 the mother noticed that the child's breasts were becoming full and rounded, the left more than the right. Some months later a scanty menstrual flow appeared, lasting 1 day. The second flow did not occur until 8 months later, but since then the periods have recurred at intervals of from two to four months, lasting from 1 to 3 days. Axillary and pubic hair appeared within the year following the menarche.

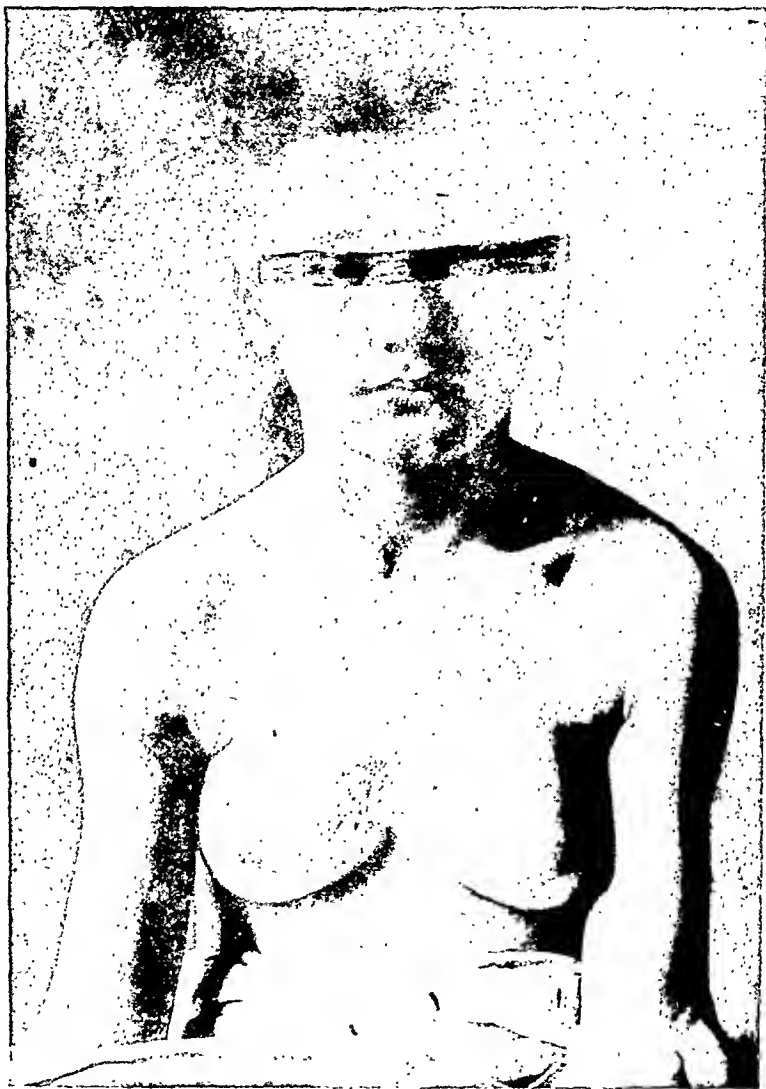


Fig. 10.—Case 7. Age 7 years. First menstruation at this age. (Harriet Lane Home Case.)

The general appearance was described as that of a girl of over 15. The face was rather mature, and the child was cooperative and intelligent. Her height was 52.5 inches. Aside from the physical characteristics above-mentioned, the gynecologic examination showed the external and internal generative organs developed far beyond those of a normal girl of her age, and resembling those of a girl at puberty. There was no



palpable evidence of a tumor. Estrogen urinary titer showed less than 3 R. U. per liter. The bone age corresponded to 12 years. The basal metabolic rate was -4. Other laboratory studies were not significant.

An exploratory laparotomy was done by Dr. R. W. TeLinde, and no evidence of any tumor was found in either ovary, though both ovaries were said to be "more yellow" than the normal adult ovary. No corpus luteum was seen, but a biopsy of the right ovary showed a mature follicle. The uterus measured 6 cm. in length, the ovaries 3 by 1½ by 1 cm.

A report from the mother on Oct. 22, 1940, stated that the child was well, and that menstruation was occurring at monthly intervals, the flow lasting 2 days.



Fig. 11.—Case 9. Age 5 years. First menstruation at 4½. (Case of Dr. T. K. Galvin.)

*Case 9.*—N. L., aged 5, was admitted on April 20, 1943, to the service of Dr. T. K. Galvin, at St. Joseph's Hospital, and I am indebted to him for permission to include the case with my own group. During the preceding year she had shown increasing development of the breasts, with also development of pubic and axillary hair, and the first menstruation had appeared in November, 1942, the flow lasting 6 days. The periods continued to recur regularly at about four-week intervals. The external genitalia were of normal puberal type. Laboratory studies were essentially negative. As the left ovary appeared somewhat larger than the right an exploratory operation was done by Dr. Galvin, but it revealed no microscopic evidence of granulosa cell tumor. The pelvic

organs at operation "were like those of a girl of 15." The left ovary was removed for microscopic examination. This showed numerous follicles in varying stages of maturation, though no corpora lutea were seen.

### Summary

While tumors of certain endocrine glands and various cerebral lesions have been reported often as causes of precocious puberty in the female, there has been little discussion in the literature concerning the constitutional type of this syndrome, probably more frequent than any other. In cases of this sort no tumor or lesion is demonstrable, nor does it manifest itself in the later course of the patient. The clinical characters of the abnormally early puberty are identical with those of normal puberty, except for the age at which they appear. Nine cases of this sort are reported in this paper, the ages of the patient being 15 months, 2, 2 years 8 months, 4,  $4\frac{1}{2}$ ,  $6\frac{1}{2}$ , 7 (2 cases) and  $7\frac{1}{2}$ .

As to why an otherwise normal puberal mechanism is awakened at an abnormally early age, no explanation seems plausible except on a chromosomal or genic basis, as is discussed in the paper, so that the designation of "constitutional" seems appropriate for this group.

Certainly cases of this type are far more common than those due to granulosa cell tumors, which gynecologists especially are apt to think of first in association with precocious puberty, often resorting to exploratory laparotomy in such cases. There can be no criticism on this point if there is a suspicious enlargement of the ovary. In the absence of any enlargement it is wiser to refrain from operation, though the patient should be re-examined at periodic intervals.

This study, particularly the microscopic examination of biopsies of the ovaries in several cases, has convinced me that, unlike the granulosa cell tumor cases, those of constitutional type may not only menstruate but also ovulate at abnormally early ages. This would explain the occurrence of pregnancy at extremely early ages, as in the remarkable case reported from Lima, Peru, in 1940, of a full-term pregnancy in a child 5 years and 8 months old.

The most important practical points in the management of these cases are (1) the psychological management, to avoid the development in the child's mind of self-consciousness or a sense of inferiority or abnormality; (2) protection against the possibility of insemination.

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26 EAST PRESTON STREET

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Leffel, James M., Masson, James C., and Dockerty, Malcolm B.: Krukenberg's Tumors, Ann. Surg. 115: 102, 1942.

The authors discuss the question of what constitutes a Krukenberg tumor? Mucus in the epithelial cells is a constant finding. "Signet-ring cells" are almost a constant finding. They feel that the term Krukenberg's tumor should include all metastatic adenocarcinomas of the ovary.

Four possible routes of metastasis are mentioned. (1) Spread by peritoneal implantation; (2) spread by lymphatic channels; (3) extension by continuity; and (4) spread by way of the blood stream. It is felt that primary adeno-"colloid" carcinoma of the ovary may rarely mimic Krukenberg's tumor. Concerning treatment, the authors feel that if the patient is a poor surgical risk or showing evidence of extensive metastasis, surgical treatment is contraindicated except for the relief of an obstruction of the genitointestinal tract. If a patient is a good surgical risk without extensive carcinomatosis then the uterus, tubes, and ovaries should be removed. An atrophic ovary should never be left intact. It is stated that a good general rule is to remove both ovaries when a solid tumor is found involving either one, particularly if the patient is near or past the menopause.

WILLIAM BERMAN

**ADRENAL-LIKE OVARIAN TUMOR ASSOCIATED WITH  
CUSHING'S SYNDROME (SO-CALLED MASCULINO-  
VOBLASTOMA, LUTEOMA, HYPERNEPHROMA,  
ADRENAL CORTICAL CARCINOMA  
OF THE OVARY)**

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**I**T IS well known that arrhenoblastomas of the ovary masculinize their hosts. However, it is not generally appreciated that other tumors of the ovary also are capable of producing similar changes in sexual characteristics. Unlike arrhenoblastomas, these tumors are associated with many of the general and metabolic symptoms, such as hypertension, cutaneous striae and diabetes, that characterize Cushing's syndrome, Cushing's disease and tumors of the adrenal cortex.

Cushing's syndrome should be distinguished from Cushing's disease. The term Cushing's syndrome should be applied solely to the now well-known clinical picture described by Cushing. This clinical picture has been found to be associated with basophilic adenomas of the anterior lobe of the pituitary body, adrenal cortical tumors, and adrenal cortical hyperplasia and tumors of thymus associated with adrenal cortical hyperplasia.<sup>12</sup> In all of these conditions Crooke's changes in the basophilic cells of the anterior lobe of the pituitary body have been found to be present.<sup>7</sup> When this clinical picture is found to be associated with a basophilic adenoma of the anterior lobe of the pituitary body, the term Cushing's disease is applicable.

The origin and nature of these tumors are difficult to determine. Their cells resemble both those of the corpus luteum and the adrenal cortex. The clinical symptoms which they produce are strikingly similar to those produced by adrenal cortical tumors and adrenal cortical hyperplasia and consequently are very similar, if not strictly identical, to those produced by basophilic adenomas of the anterior lobe of the pituitary body (Cushing's disease).

It is not surprising, therefore, that pathologists have had difficulty in inventing suitable names by which these neoplasms can be designated. Glynn lumped them into one group to which he referred as "yellow tumors of the ovary." Others, impressed by the histologic similarity of the tumor cells to either the cells of the corpus luteum or to the cells of the adrenal cortex, have introduced such terms as "luteoma,"<sup>21, 27</sup> "luteoblastoma," "hypernephroma" and "adrenal cortical carcinoma" of ovarian origin. The term "luteoma"<sup>28</sup> is particularly unfortunate as it has been applied not only to the group of neoplasms under discussion but also to granulosa cell tumors, the cells of which have undergone

luteinization. Rottino and McGrath tried to escape from the horns of the dilemma by introducing the noncommittal Latin-Greek hybrid "masculinovoblastoma." For various reasons, some of which will be apparent later, none of these designations is satisfactory. Rather than introduce further confusion in nomenclature and yet avoid the difficulties which arise from use of any one term to the exclusion of the others, we have decided to speak of them as "adrenal-like ovarian tumors." To date, thirteen well authenticated cases of such adrenal-like ovarian tumors have been reported in addition to the one which we are reporting. Rakoff<sup>19</sup> also speaks of another case which according to a personal communication will be reported in detail later.

### Report of Case

The patient, a white girl aged sixteen years, of Polish parentage, came to the Mayo Clinic August 5, 1942, because of amenorrhea and hirsutism. She was under the care of Dr. L. W. Pollock, with whose cooperation this report is made. One sister was said to have had a similar disorder. As far as could be learned her puberty was normal. The menses began at about the age of eleven and at first were regular and normal. When she was about thirteen years of age the flow became somewhat scanty and sometimes she would skip periods for two or three months at a time. Finally, in October, 1940, at the age of fourteen years, her menses ceased entirely. There were no hot flushes. At the same time coarse, black hair appeared on the face, arms, legs and abdomen so that "hair remover" and finally a razor had to be used. Simultaneously, she gained in weight and her face became full and round. Headaches became very troublesome. By the spring of 1942, her appearance had changed to such an extent that one of her sisters who had been away for some months had difficulty in recognizing her.

Except for a reactive mental depression the girl's psychologic attitude was remarkably good under the circumstances. She made good grades in school, generally a "B" average, and she enjoyed her studies. Specific information regarding her sexual proclivities was difficult to obtain, but her mother stated that she had not noticed anything strikingly abnormal in the girl's behavior toward associates of either sex. She preferred the company of girls and disliked to attend parties and social functions if boys were going to be present. Her relations to the latter were "strictly friendly."

During the course of her illness she had consulted several physicians, and as her condition seemed to be becoming progressively more alarming she decided to come to the clinic.

The patient gave the impression that she was sexually neuter. She objected slightly to being examined, was a bit sullen, but on the whole there was nothing notably abnormal in her behavior in the examining room. She was 5 feet 2 inches (127 cm.) tall and she weighed 141 pounds (64 kg.). Her voice seemed to be somewhat low pitched but the Adam's apple was not abnormally prominent.

When she was undressed, her body conformation and general appearance were distinctly but not entirely masculine in type (Fig. 1). The skeletal framework was heavy and sturdy and the musculature was exceptionally well developed and conspicuous. Her athletic appearance was accentuated by a strong lower jaw, a prominent mental protuber-

ances and a cleft chin. The shoulders were square and broad and the trapezius muscles stood out prominently. The characteristic fat deposits (for example, those above and below the clavicle) which contribute so much to the femininity of the normal woman's appearance were largely, but not entirely, absent. The abdomen protruded and the hips were narrow, especially below the trochanters. A suggestion of a "buffalo hump" was apparent in the cervicothoracic region.

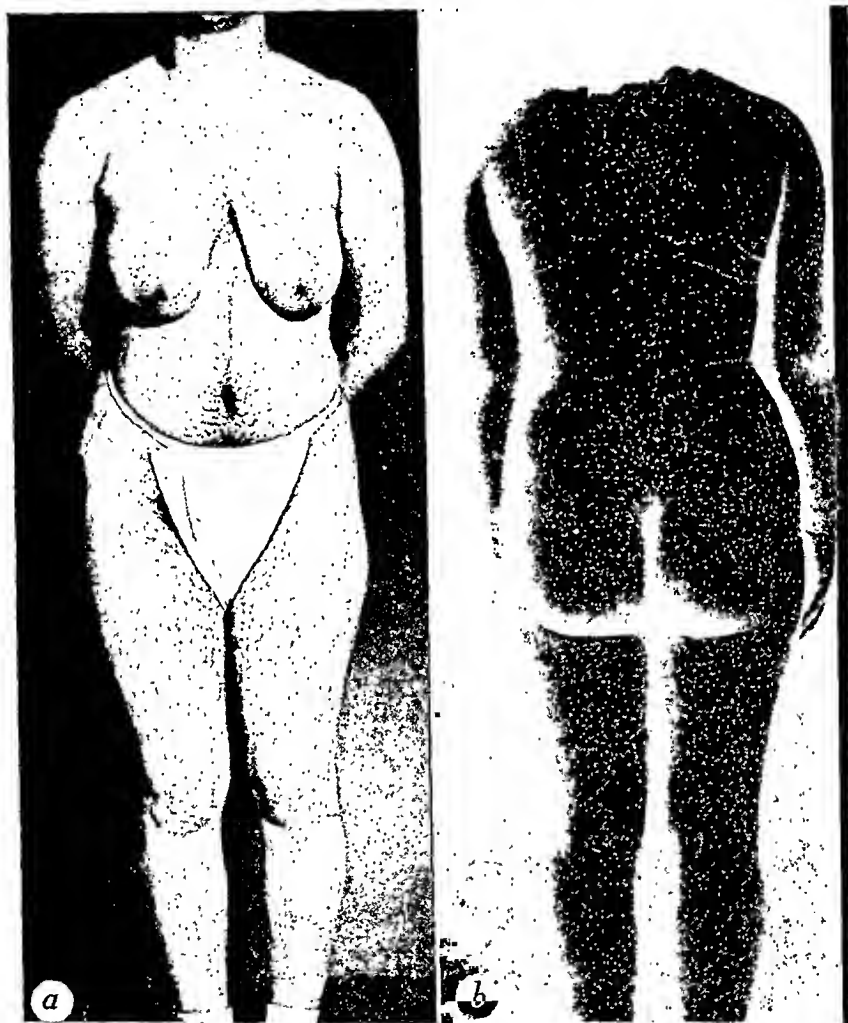


Fig. 1.—Appearance of patient's body before operation.

Her face (Fig. 2) was slightly rounded; the palpebral fissures were narrowed because of drooping upper lids and the corners of the mouth were depressed. All of these factors contributed to give her a "down-at-the-mouth" look. The skin was dry and rough because of extensive areas of keratosis pilaris, and between the shoulders and down the back there was a well-marked acneform eruption. Below the iliac crests there were well-defined purplish striations. In color, the skin was somewhat florid and this was especially noticeable in the face. On the arms, legs, thorax and abdomen, back and buttocks there was a prominent overgrowth of coarse dark hair. At the temples the hair of the scalp was

beginning to recede, side burns extended down the cheeks, and the eyebrows met at the midline. Curiously, there was only a trace of a mustache. The breasts were large, pendulous and flabby and were particularly conspicuous because of exceptionally large, florid and pigmented areolae. The clitoris was about three times the normal size. In millimeters of mercury, the blood pressure was 160 systolic and 110 diastolic. The ocular fundi and the retinal vessels appeared to be normal.



Fig. 2.—Appearance of patient's face; *a*, before operation; *b*, five months after operation.

As the examination proceeded, the possibility of an adrenal cortical tumor naturally suggested itself, so that one was mentally prepared, on examining the abdomen, to find a mass in either renal region; however, the upper part of the abdomen was disappointingly normal and when, on bimanual pelvic examination, the mass, which by all the rules of the game should have been situated beneath the costal margins, was encountered deep in the pelvis, the resulting surprise was decidedly disconcerting. Nevertheless, as one reviewed the history of the girl's illness and re-examined her physically, the conviction grew that she almost certainly had to have a tumor comprised of hyperfunctioning adrenal cortical tissue. If this were the case the pelvic tumor would have to be an incidental abnormality, such as an ovarian cyst unrelated to the clinical picture or an aberrant adrenal cortical tumor. With these thoughts in mind we conducted the following laboratory studies:

Routine urinalyses, flocculation tests for syphilis, roentgenograms of the skull and thorax gave results that were either negative or normal. A soft tissue mass containing zones of calcium was noted in the roentgenograms of the pelvis. None of the roentgenograms showed any evidence of osteoporosis. The value for the hemoglobin was 17.0 Gm. per 100 c.c. of blood. The leucocytes numbered 9,900 per cubic millimeter. Unfortunately, an erythrocyte count was not made nor were the blood smears studied hematologically. Chemical studies of the blood gave the

following values, all of which are expressed in milligrams per 100c.c.: blood sugar, 68; plasma chlorides (as NaCl), 594; serum sodium, 342, serum potassium, 20.2. The carbon-dioxide combining power of the plasma was 52.2 volumes per cent. The urinary excretion of 17-ketosteroids per twenty-four hours, as determined by the Callow colorimetric method, was 54.6 mg. (The normal value for women is about 10.0 mg. in twenty-four hours; the range is 6 to 17 mg.) Urinary assays for estrin (estrogenic substance) and normal amounts of prolactin (gonadotropic substance)\* gave the following values in rat units per twenty-four hours: estrin 19; prolactin less than 10.

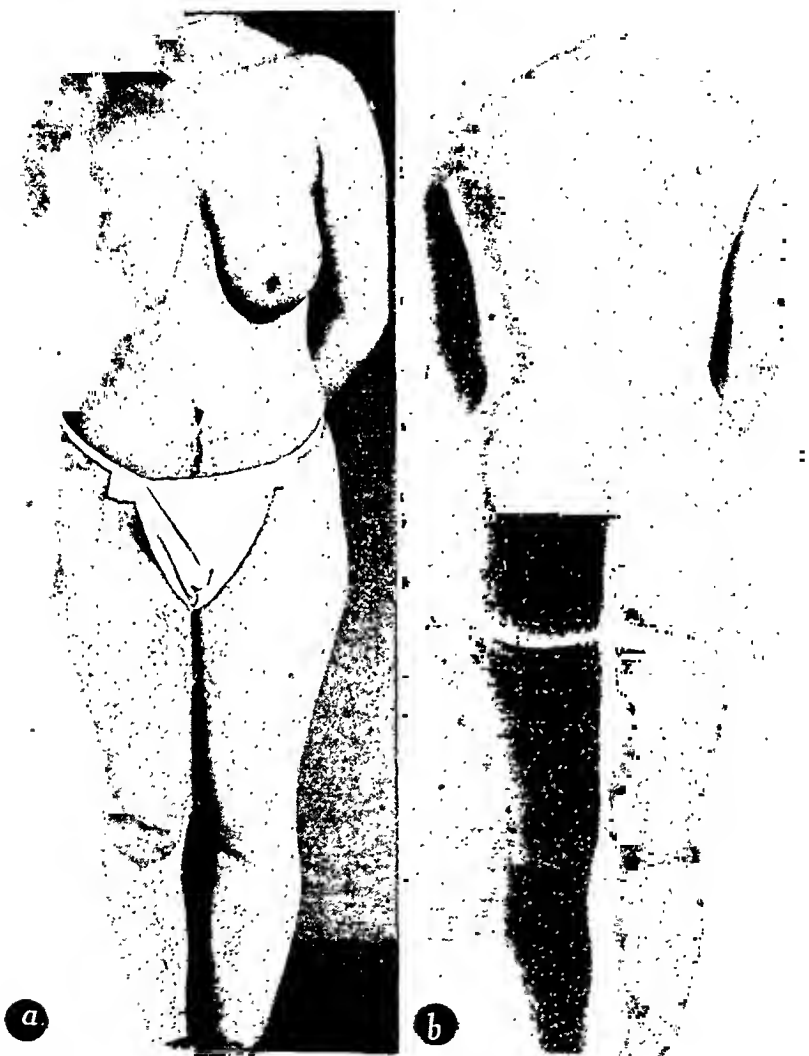


Fig. 3.—Appearance of patient's body five months after operation.

The results of these studies strengthened our tentative diagnostic opinion. Consequently one of us (E. J. K.) felt that a probable diagnosis of "adrenal cortical tumor of the ovary" was warranted.† Accordingly, it was decided to explore the pelvis surgically, first treating the patient

\*Frank technique.

†Not being handicapped by too much knowledge of unusual ovarian tumors and being skeptical that "luteomas" ever caused masculinity. I did not have too many misgivings when I offered this somewhat unusual diagnostic suggestion.—E. J. K.



preoperatively as though she had an adrenal cortical tumor and then, if the biopsy of the tumor revealed an adrenal type of cell, to continue with the postoperative treatment which has been used at the clinic in cases of this type of tumor. (Previous experience with tumors of the adrenal cortex has more than justified the wisdom of this procedure.)<sup>13, 26</sup>

Accordingly, on August 19, 1942, an exploration of the pelvis through a low midline incision was made by one of us (J. T. P.). A lobulated encapsulated tumor about the size of a cantaloupe was found. The tumor was yellowish in color, firm in consistency and free from any attachments except the right Fallopian tube which lay stretched out over the capsule. The tumor, which appeared to take the place of the right ovary, was accordingly removed, along with the right Fallopian tube and the appendix.

Examination of fresh sections of the tumor prepared by the rapid freezing technique and stained with polychrome methylene blue resulted in a diagnosis of "probable adrenal cortical tumor of ovarian origin," and the patient was accordingly treated postoperatively as had been planned.\*

The patient had an uneventful convalescence. At the time of her dismissal her appearance had started to change for the better.

On January 4, 1943, the patient returned for re-examination as requested. During the intervening five months many of the manifestations of her illness had disappeared. One month after her operation she had a normal menstrual period and her periods remained regular and normal thereafter. A remarkable change in her appearance has occurred (Figs. 2, 3A and B). The abnormal cutaneous hair was almost entirely gone. There remained a masculine pubic hair line, the faintest suggestion of a mustache and three or four short black hairs between the breasts. She stated that after her operation the hair of the scalp came out and was being replaced by a finer, more feminine type of hair. Her mannerisms were now distinctly feminine. She had no complaints except that she became tired much more easily than she had previously. She also remarked that her grades in school were not as good as they had been and that she had lost interest in her school work in general. Her mother called attention to the fact that whereas previously the patient had never been afraid of anything, now she became frightened rather easily and objected to being left alone in the house. Her weight was now 132 pounds (59.9 kg); the blood pressure varied from 138 mm. to 140 mm. systolic and from 80 mm. to 100 mm. diastolic. The value for urinary 17-ketosteroids was 2.6 mg. per twenty-four hours.

Grossly, the tumor measured 15 by 14 by 9 cm. and weighed 650 Gm. It was orange-yellow in color, coarsely lobulated in outline, and entirely invested by a smooth, glistening, grayish capsule which was free from adhesions. A pedicle measuring 6 cm. along its edge of attachment and 1 cm. in width consisted of the mesosalpinx which, like the right Fallopian tube, lay stretched out over the surface of the tumor. Surfaces made by cutting (Fig. 4) revealed that the substance of the tumor was bright yellow in color except for several small zones where hemorrhage

\*The preoperative and postoperative treatment was as follows: Immediately before and after the operation the patient was given 1 liter of physiologic salt solution intravenously. Two liters were given daily thereafter for two days and one liter daily for two additional days. Five milligrams of desoxycorticosterone acetate was given daily for four days, beginning with the day of the operation. Twenty cubic centimeters of adrenal cortical extract was given when the patient returned from the operating room; 5 c.c. every three hours thereafter until eleven doses had been given, whereupon the dose was reduced to 5 c.c. every six hours for the next thirty-six hours. By this time the patient was well on the road to recovery and hormonal therapy was discontinued but physiologic salt solution was administered by mouth for the next two days.

imparted a dark, reddish appearance. Consistency was solid throughout. A pronounced degree of lobulation was present, the more superficial nodules of which corresponded to the external bosselations described previously. In the center of the mass was a calcified nodule, 2 cm. in diameter, apparently representing the zone of radio-opacity noted by the roentgenologists.

In preparations stained with hematoxylin and eosin the outstanding microscopic characteristic of the tumor was an essential composition of large pale polygonal cells arranged in anastomosing cords, sheets and irregular strands but rarely in structures approaching an acinar arrangement. Cellular groups were aggregated to form lobules of variable size and between these lobules bundles of fibrous tissue formed a coarse type of scaffolding. From these fibrous tissue septa small groups of fibroblasts spread in a radiating manner to surround the smaller units of tumor cells. Focal nests of lymphocytes were seen in the stroma (Fig. 5a). With higher magnification, the tumor cells were seen to be

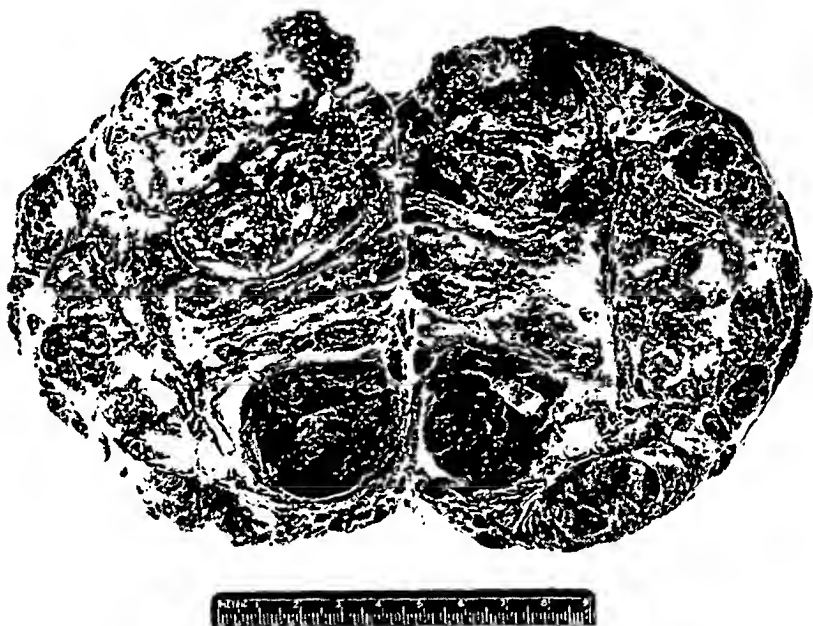


Fig. 4.—Cut surface of tumor; the dark areas represent hemorrhage within the tumor substance; remaining portion was of a bright orange-yellow color.

epithelial-like, large and polygonal, with fairly sharp outlines. Cytoplasm was voluminous and filled with rounded vacuoles which varied in size and number directly with the size of the individual tumor cells (Fig. 5b). Nuclei were large, centrally placed, and each possessed a sharp nuclear membrane. Nucleoli were prominent and usually single, but multiple nucleoli sometimes were observed. Multinucleated cells were occasionally noted in normal and in giant cell forms and this picture recalled a similar common observation in adrenal cortical tumors (Fig. 6). Mitosis was fairly frequent. Because of the cellularity, mitotic activity, size of nucleoli and variation in staining qualities of cells, the neoplasm was adjudged malignant grade 2 on the basis of 1 to 4 (by the method of Broders). Blood vessels were numerous and the larger ones were well formed. The smaller ones coursing between the smaller columns of tumor cells were often represented by blood filled spaces lined by a single layer of endothelium.

Special stains for lipid demonstrated large amounts of this substance in the cytoplasm of the polyhedral cells (Fig. 7A). It varied in amount and one gathered from a study of the slides that many of the tumor cells were enlarged chiefly because of their high content of lipid. Many of the smaller tumor cells appeared to be arranged in groups or islands and in these the fatty droplets were small in size and few in number.

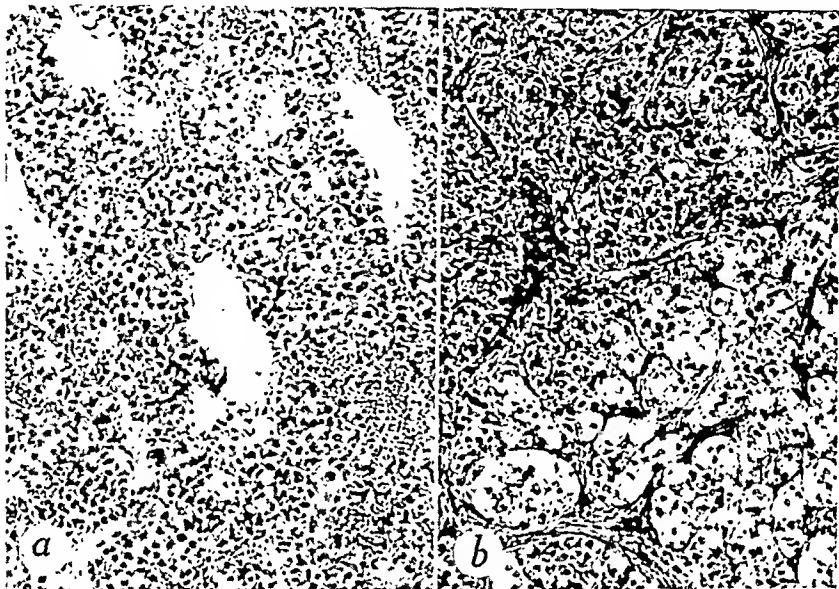


Fig. 5.—*a*, Anastomosing cords of tumor cells recall the structure of the suprarenal cortical tumors; blood vascular spaces are abundant and there are occasional accumulations of lymphocytes; stained with hematoxylin and eosin ( $\times 100$ ); *b*, large, polygonal, pale and vacuolated tumor cells; some variation in size can be noted (the largest cells contain the most lipid); definite organization into cords and strands is apparent and the individual units are separated by fine bands of connective tissue; stained with hematoxylin and eosin ( $\times 100$ ).

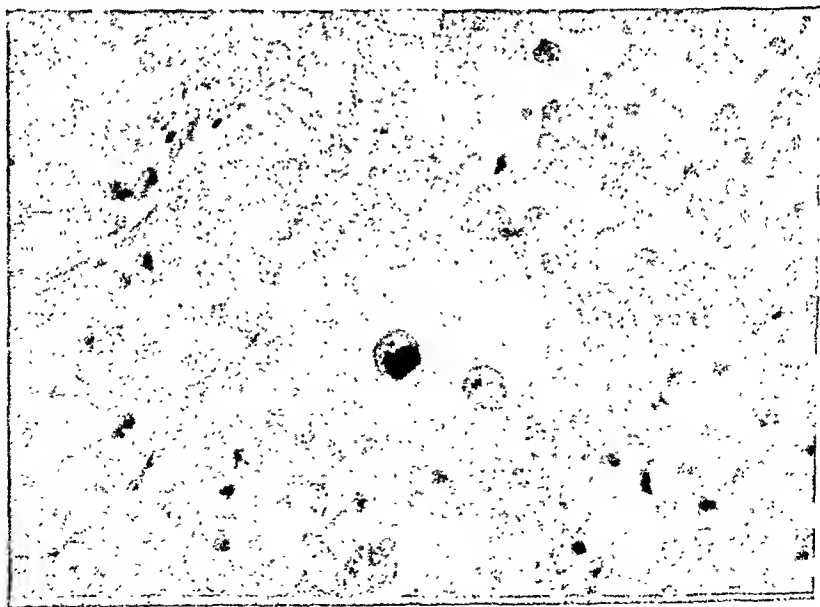


Fig. 6.—Much nucleated giant cells in this tumor appear to relate it to tumors of adrenal-cortical origin; stained with hematoxylin and eosin ( $\times 280$ ).

Blocks of tissue preserved in absolute alcohol were stained for glycogen. This substance was demonstrated in different portions of the tumor (Fig. 7*B*) but in a rather spotty distribution. Its presence in the cytoplasm in general was in inverse proportion to the amount of lipoid. Sections made from blocks of tissue that had been fixed in Zenker's solution were stained with Ponceau-fuchsin stain.<sup>9</sup> Many of the cells contained the specific granules that are regarded by Broster and Vines as indicative of "androgenic" tissue (Fig. 8*A*). Slides made from de-

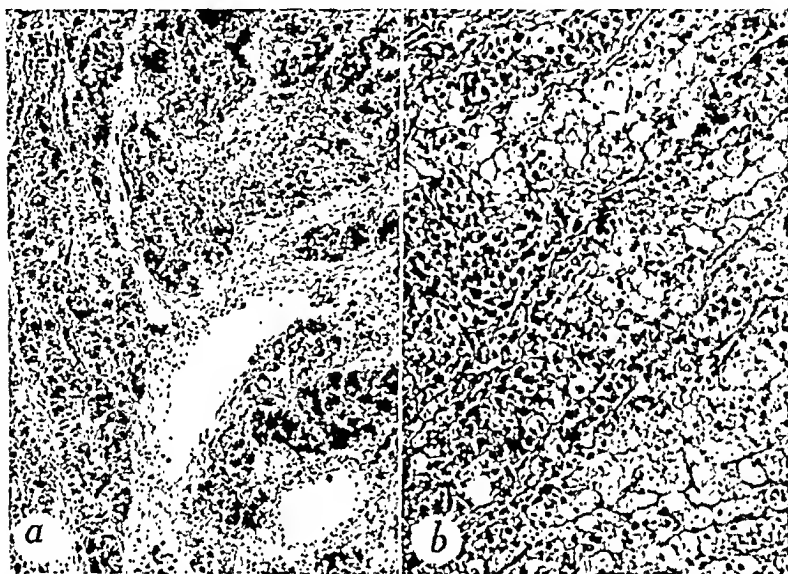


Fig. 7.—*a*, The high lipoid content of the tumor cells is well shown; stained with sudan III ( $\times 50$ ); *b*, a positive test for glycogen is indicated by the small, darkly stained tumor cells; stained with carmine ( $\times 95$ ).

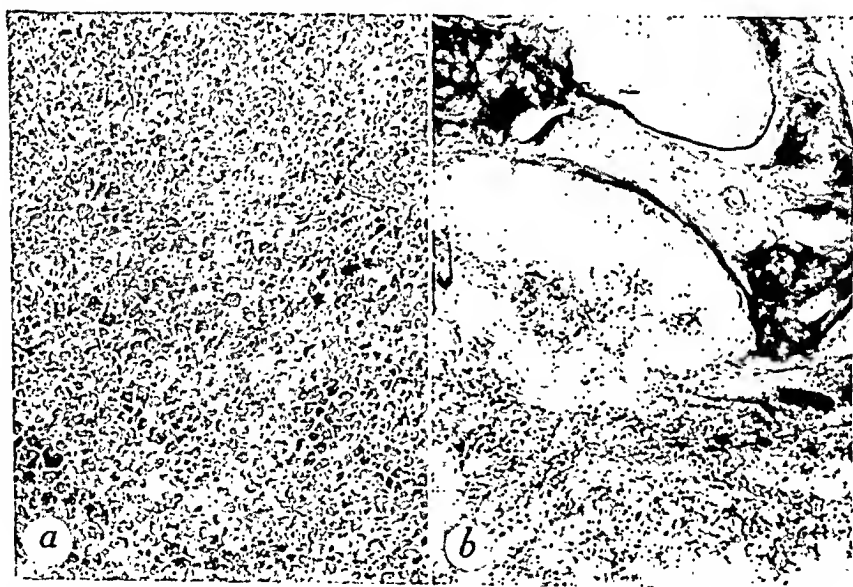


Fig. 8.—*a*, Darkened cells indicate a positive fuchsinophilic reaction; stained with Ponceau's fuchsin stain ( $\times 95$ ); *b*, ossified nodule from center of tumor showing well-formed bony trabeculae and marrow elements; stained with hematoxylin and eosin ( $\times 85$ ).

calcified portions of the calcified nodule noted in the roentgenogram revealed irregular calcification and also focal ossification. The osseous tissue appeared to be true bone with well formed haversian canals and islands of fairly normal looking bone marrow (Fig. 8B). The capsule of the tumor appeared everywhere intact superficially but more deeply it revealed small islands of invasion by neoplastic tissue. In most of the sections studied, tissue resembling ovarian stroma could be identified and in one the presence of a corpus fibrosum and a primordial follicle established beyond question of doubt that the neoplasm was of ovarian origin (Fig. 9). Except for the presence of bone and ovarian tissue, the preceding description could be applied to the general run of adrenal cortical tumors.



Fig. 9.—Portion of capsule of tumor; the corpus fibrosum and primordial follicle identify the tissue as being truly ovarian, stained with hematoxylin and eosin ( $\times 80$ ).

### Comment on Cases

Tables I and II summarize the clinical and pathologic data in the case which we have just reported (case 14) and in thirteen additional cases previously reported in the literature. Certain features are deserving of special emphasis. Hirsutism was present in all fourteen cases and varied in duration from nine months to thirteen years. A masculine pattern of distribution of hair usually was noted. This was emphasized in four instances by an observed recession of the hair line along the forehead, with the notation that the patients were partially bald.

In ten of the fourteen cases the habitus was described as being of masculine type with pronounced development of the muscles of the shoulder girdle. In eight of the fourteen cases there was a definite and sometimes pronounced gain in body weight. Moreover, in the majority of the observed instances the obesity was more or less localized to the face, cervical region and pectoral girdle.

Blood pressure readings were recorded in six of the twelve cases that were reported more recently. In four of these cases, hypertension was present with systolic pressures in excess of 140 mm. or diastolic pressures of more than 90 mm. of mercury. In the case we have just reported, postoperative readings of the arterial blood pressure indicated a moderate drop in both systolic and diastolic pressures from distinctly high preoperative levels. This finding indicates that in some way the ovarian tumor was responsible for the observed arterial hypertension.

Diabetes or a diabetic tendency was of relatively frequent occurrence. In one of the fourteen cases, clinically recognized diabetes had been present for six years. Another patient had a trace of sugar in the urine but was apparently not otherwise investigated for evidence of diabetes. In another case the concentration of blood sugar was 150 mg. per 100 c.c. and in two additional cases the presence of subclinical diabetes was indicated by abnormal glucose tolerance curves.

Hematologic observations suggesting polycythemia vera were unusually common in the group. Blood counts were recorded in eight of the fourteen cases and in four of these the number of erythrocytes exceeded 5,000,000 per cubic millimeter of blood. In one of these cases the erythrocytes numbered almost 9,000,000 per cubic millimeter and dropped to 6,000,000 after removal of the tumor.

In a number of instances, the blood and urine were studied for various hormonal substances. In the case reported by Saphir and Parker (case 5) the urine contained 5,000 mouse units of estrogenic substance per liter and 66 mouse units of gonadotropic substance per liter. In another case, reported by Novak and Wallis (case 6), estrogenic substance could not be detected in the urine before operation but 200 mouse units per liter were found afterwards. In the case reported by Maxwell (case 7), 40 mouse units of estrogen were present in 1 liter of urine but gonadotropic substance was absent. Quantitative estimation of androgenic material by the Capon method was made in one of the two cases reported by Rottino and McGrath. Values obtained were 17.3 and 15.7 international units. In the same case, the value for estrogens was 3.3 rat units per liter.

From the pathologic standpoint, all of the tumors have been unilateral with but one exception, in which both the right and left ovary equally shared the dubious honor of being host. Size has varied from nodules of microscopic dimensions to masses measuring 16 by 14 by 9 cm. The tumors were for the most part yellowish in color and encapsulation was the rule in practically all recorded instances. Microscopically, the tumors were composed of large, pale, polyhedral, epithelial-like cells disposed in cords and anastomosing strands. Large amounts of intracellular lipid material were noted in nearly all cases and intercellular glycogen was occasionally found to be present. Ponceau-fuchsin stains were employed in most of the cases recently reported and these tests yielded positive results in three cases. In twelve of the fourteen cases,

TABLE I. COMPARATIVE CLINICAL DATA

CASE	AUTHOR	AGE (YR.)	PARTY	HIR-SUTISM	MASCU-LINE HABITUS	VOCAL CHANGES	HYPER-TROPHY OF CLITORIS	OBESITY OR GAIN IN WEIGHT	AMENOR-RHEA	HYPERTEN-SION	DIABETES	OUTCOME
1	Bovin, 1908	28	Multiparous	+ (6 years)	Not stated	Not stated	Not stated	Not stated	+	(7 years)	Not stated	Recovery. Patient later became pregnant.
2	Bingel, 1924	47	Para iv	+ (13 years) Partially bald	+	(10 years)	Not stated	+	+	(13 years)	(6 years)	Feminine habitus in 3 years. (Partial relapse.)
3	Sellheim, 1925	49	Para ii	+ (6 years) Partially bald	+	(6 years)	+	+	+	(6 years)	Not stated	Feminine habitus in 1 year.
4	Cosnesco et al., 1931	34	Para 0	+ (5 years) Partially bald	+	(5 years)	+	0	+	(7 years)	Not stated	Completely feminine in 2½ years.
5	Saphir and Parker, 1936	15	Para 0	+ (1 year)	0	+	+	(1 year)	+	(1 year)	Blood pressure 110 to 130 mm. systolic and 70 mm. diastolic	Partial return to normal in 1 year.
6	Novak and Wallis, 1937	32	Para 0	+ (2 years)	+	(Months)	+	Slight	+	(2 years)	Fasting blood sugar 150 mg. per 100 c.c.	Normal feminine habitus in 1 year.
7	Maxwell, 1937	62	Para 0	+ (5 years) Partially bald	+	(10 years)	+	Not stated	0 (postmenopausal)	Blood pressure 200/100	Diabetic type of glucose tolerance curve	Improvement in 4 months.

TABLE I—CONT'D

	8	Novak, 1938	37	Not stated	+	+	+	Voice deep but feini- nine	+	+	+	(3 years)	Blood pres- sure 130/90	0	Normal habitus in 3 years.
	9	Novak, 1938	27	Not stated	+	+	+	(9 mo.)	+	+	Not stated	(1 year)	Not stated	0	Menses became normal within 3 months.
	10	Rottino and McGrath, 1939	23	Para i	+	(4 years)	+	+	+	+	(5 years)	(3 years)	0	Diabetic type of glucose tolerance curve	Seminormal hab- itus in 18 months. Blood sugar curve still abnormal at 6 months.
	11	Rottino and McGrath, 1939	30	Para 0	0	+	+	(5 years)	+	+	(caused by ascites?)	(after hys- terec- tomy)	Blood pres- sure 130/70	0	Temporary im- provement; re- currence; death in 4 years.
	12	Bauer, 1939	32	Para i	Not stated	+	+	0	+	+	+	(3 years)	Not stated	?	Died at operation.
	13	Blackmun, 1942	23	Para 0	+	(3 years)	+	Voice husky	+	+	(30 lb. gain)	(1 year)	Not stated	Diabetic type of glucose tol- erance curve	Improvement in 1 year.
	14	Dockerty and Kepler, 1943*	16	Para 0	+	(1 year)	+	0	+	+	(20 lb. gain)	(2 years)	Blood pres- sure 160/110	0	---

**\*\*This case has been reported in the present paper.**



TABLE II. COMPARATIVE PATHOLOGIC DATA

CASE	AUTHOR	SIDE INVOLVED	SIZE, CM.	COLOR	PRES- ENCE OF CAPSULE	TRABEC- ULATION	PRES- ENCE OF LIPOID	FUCHSIN- OPHILUS GRANULES	PRES- ENCE OF GLYCOGEN	IDENTIFI- CATION OF OVARIAN ORIGIN	SIGNIFICANT LAB- ORATORY DATA
1	Bovin, 1908	Left	8 by 8 by 6	Yellow	+	+	+	Test not then avail- able	Not stated	+	0
2	Bingel, 1924	Right	9 by 4 by 4	Yellow	+	+	+	Test not then avail- able	Not stated	Not stated	Erythrocyte count, 8,900,000
3	Sellheim, 1925	Left	"Chestnut," 1 1/2 by 1 1/2 by 1 1/2	Grayish- red	+	+	0	Test not then avail- able	0	Not stated	0
4	Cosacesco et al., 1931	Left	Nodule in wall of cyst 5 cm. in diameter	Yellow	+	+	+	Test not then avail- able	Not stated	+	0
5	Saphir and Parker, 1936	Right	Microscopic.	Not stat- ed	+	+	+	Not stated	Not stated	+	Increase in urinary es- trogens
6	Novak and Wallis, 1937	Right	13 by 8 by 5	Orange- yellow	+	+	+	Not stated	Not stated	+	Erythrocyte count, 6,600,000

TABLE II—CONT'D

7	Maxwell, 1937	Left	Microscopic	Not stated	+	Not stated	+	Not stated	Not stated	+	Increase in urinary estrogens; erythrocyte count, 6,100,000
8	Novak, 1938	Right	6 (diam.)	Orange	+	+	+	Not stated	Not stated	+	0
9	Novak, 1938	Right	2 (diam.)	Yellow	+	+	+	Not stated	Not stated	+	0
10	Rottino and McGrath, 1939	Right	4 by 1.5 by 1.5	Orange	+	+	+	0	0	+	Urine positive for estrogens and gonadotropins
11	Rottino and McGrath, 1939	Bilateral	3 (diam.)	Orange	Not stated	+	+	Not stated	Not stated	+	0
12	Bauer, 1939	Left	14 by 13 by 5	Not stated	Not stated	+	+	+	Not stated	+	0
13	Blackmun, 1942	Left	4 (diam.)	Yellowish gray	+	+	+	+	Not stated	+	0
14	Doekerty and Kepler, 1943*	Right	15 by 14 by 9	Yellow	+	+	+	+	+	+	Value for hemoglobin 17 Gm. per 100 c.c. of blood

\*This case has been reported in the present paper.

the presence of ovarian tissue was demonstrated microscopically in the tumor capsule. In another case there was gross evidence for an ovarian point of origin. In the case reported by Bovin (case 1), ovarian involvement was very definite, but an origin from the homolateral broad ligament could not be entirely excluded.

As is true with most neoplastic newcomers, there was much hesitation in deciding the question of malignancy. The case reported by Rottino and McGrath (case 10) provided an answer or the confirmation when the patient died of metastasis. In this case the tumors (bilateral) differed in no essential microscopic detail from many of the others which had been regarded by the authors as being benign. In the case that we have reported in this paper (case 14 in the tables) the malignancy of the tumor was grade 2 according to the method of Broders.

The tumors under consideration may be studied from three distinct angles, namely: (1) structure and histogenesis; (2) clinical manifestations, and (3) pathologic physiology as shown by the presence of hormonal substances in the urine. Each of these three approaches has its distinct limitations. Consequently, any theory regarding the nature of these tumors must take into consideration the factual data derived from all three types of approach.

*Histogenesis.*—Histologically, these tumors conceivably might arise from one of the following structures: (1) the adult corpus luteum; (2) a pre-existing granulosa-cell tumor; (3) an adrenal cortical ovarian rest, and (4) through excessive development of certain cellular elements (adrenal cortical?) in a teratomatous growth. In 1921, Ernest Glynn analyzed critically most of the literature on yellow tumors of the ovary including a number of lesions that had been labelled "hypernephromas" and ascribed in point of origin to adrenal cortical rests in the ovary. Glynn's investigation led him to the belief that these tumors had no connection with adrenal tissue whatsoever, but were, for the most part, derived from the corpus luteum. He based his arguments on clinical as well as histologic grounds, and pointed out that the tumors never cause masculinization as did adrenal cortical tumors. The case reported by Bingel (case 2) apparently escaped his notice and the masculinizing tumor in the case reported by Bovin (case 1) he relegated to an origin in the broad ligament, with secondary invasion of the ovary. (He apparently was ready in this latter case to concede an origin from heterotopic adrenal tissue.) The cases reported by Bovin and by Bingel (cases 1 and 2) were the only two which antedated the publication of Glynn's splendid article. In the light of recent investigations, it now appears that several of Glynn's "hypernephromas" conceivably may have been of corpus luteum origin. Two appear to be undoubted examples of compound lutein cysts associated with hydatid mole. Pathologically, however, most of the remainder clearly represent examples of luteinized granulosa-cell tumors with clinical symptoms of feminization

and not masculinization. Were Glynn now to analyze the examples of yellow masculinizing ovarian tumors which have been described since 1921, there is no doubt that some of his arguments for a corpus luteum origin would lose much of their force. Schiller logically pointed out that the corpus luteum is ordinarily a transient structure derived from two pre-existing cellular elements in the ovary, namely, granulosa cells and theca cells. From the granulosa cells are derived the well-known granulosa-cell tumors which may in some cases become luteinized, in which case they have been called "luteomas." From the theca cells arise the theca cell tumors. Both of these tumors are "feminizing." Neither is associated with virilism or the other symptoms which accompany the tumors under consideration. Furthermore, according to Schiller, it seems highly unlikely that any type of tumor composed of corpus luteum cells could possibly produce virilism, striae, hypertension, osteoporosis, diabetes (that is, Cushing's syndrome) when one considers what is known concerning the hormonal function of the corpus luteum. Certainly these symptoms are entirely out of line with what one would expect from hyperfunctioning cells of the corpus luteum.\*

Both the gross appearance and the histologic structure of the present group of tumors suggest an adrenal cortical origin. If this were the case one would expect that the incidence of these tumors could be correlated with the incidence of adrenal rests within the substance of the ovary. However, according to the best figures available, it is impossible to make such a correlation. In fact, it appears that adrenal rests within the ovary occur even less frequently than do these adrenal-like tumors.† Adrenal cortical rests occur elsewhere in the body with considerable frequency,<sup>16</sup> and there are a few clear-cut examples of ectopic adrenal cortical tumors that have arisen from such rests.<sup>14</sup> However, as yet there is no conclusive evidence that ectopic adrenal tissue within the ovary has given rise to an ectopic adrenal tumor, unless the tumors under consideration ultimately will be proved to be examples of such an occurrence.

The presence of glycogen, noted in several of these tumors, has led to the belief that the tumors were of adrenal origin. However, we now know that the corpus luteum, on the one hand, and adrenal adenocarcinoma, on the other, also contain small or large amounts of this substance. It is doubtful, therefore, if the presence of glycogen in any given tumor can be taken as evidence of its histogenesis. This argument applies with equal force to a positive reaction with the Ponceau-fuchs stain. This stain, originally considered specific for cells of the andro-

\*On the other hand, many of the symptoms of adrenal cortical tumor are not those that one would expect from what is known regarding the physiology of the adrenal cortex.

†Grollman, however, expressed the opinion that adrenal rests within the ovary occur fairly commonly during infancy, but that they are composed of androgenic tissue and regress during childhood along with the androgenic tissue of the adrenal cortex. Incidentally, according to the same author, it is this androgenic tissue, which fails to regress and ultimately becomes hyperplastic or neoplastic, that gives rise to the sexual abnormalities seen in conjunction with adrenal cortical tumors or with conception conveniently ignores many of the metabolic symptoms, such as diabetes, hypertension and osteoporosis and others that commonly occur in conjunction with either adrenal cortical neoplasms or hyperplastic lesions.

genic adrenal type has been found to react positively with the cells of the corpus luteum. Sharp cytoplasmic outlines of tumor cells have been interpreted as indicating an adrenal origin for these ovarian tumors but the degree of sharpness has been found to depend more upon the size and the number of lipoid droplets than upon any fundamental difference between an adrenal cortical and a corpus luteum cell.

It may thus be seen that from the standpoint of pure cytology the origin of these tumors is a histogenic jigsaw puzzle. In the case that we have reported, the finding of well-formed, marrow-bearing bone early raised our hopes that we had the answer to this puzzle in a clear teratomatous origin. Careful search, however, failed to reveal the presence of any other unusual tissue types and we were left to face the bleak fact that calcification and even ossification may occur in any type of neoplasm. Consequently, the theory of a teratomatous origin must remain as an unproved possibility.

*Clinical Manifestations.*—The endocrine symptoms of adrenal cortical tumors vary qualitatively and quantitatively in individual cases. A comparable variability appears, possibly to a lesser extent, to run through the group of ovarian tumors under consideration. Nevertheless, in spite of this variability, the composite clinical picture of the one group has much in common with the composite clinical picture of the other. For example, each group of tumors tends to be characterized by pathognomonic changes in the facies and habitus which were so graphically described by Cushing. In addition, one can mention amenorrhea, hirsutism, acne, enlargement of the clitoris and other symptoms usually considered to be indicative of masculinization. Of particular interest, however, is the occurrence in each group of an unusual combination of symptoms, namely, hypertension, polycythemia and diabetes. Polycythemia, for example, although not a particularly common symptom of adrenal cortical tumor, may be present to such an extent that all the common hematologic criteria necessary for the diagnosis of polycythemia vera can be obtained. The occurrence of severe polycythemia (approximately 9,000,000 erythrocytes per cubic millimeter) in case 2 in Table II is, therefore, particularly suggestive that in this instance the tumor was in fact a tumor of the adrenal cortex. Diabetes, likewise, does not occur regularly in cases of adrenal cortical tumor. Nevertheless, in a case recently reported by Sprague, Priestley and Doekerty it was the only endocrine manifestation of an adrenal cortical tumor. The relatively high incidence of diabetes in the fourteen cases listed in Table I has already been noted.\* The foregoing remarks relative to polycythemia and diabetes are equally applicable to hyperten-

\*The occurrence of diabetes in this type of case suggests an overproduction of the adrenal "diabetogenic hormone" (11 dehydro-17 hydroxy corticosterone or compound E of Kendall and compound Fa of Reichstein) by the tumor, whereas the presence of hypertension might be taken as indicative of an excessive production of some compound similar to desoxycorticosterone. As yet there is no adequate explanation for the occurrence of polycythemia. For a stimulating discussion of the pathologic physiology of Cushing's syndrome and allied disorders the reader is referred to Fuller Albright's article in the 1943 *Harvey Lectures*.

sion. All three of these symptoms, which dovetail nicely with what is known regarding the normal and abnormal physiology of the adrenal cortex, strongly suggest that, if these ovarian tumors are not in reality ectopic adrenal cortical tumors, they function as such and have common pathophysiologic denominators with them.

At this point it is well to re-emphasize that none of the metabolic symptoms which have been mentioned occur regularly in conjunction with arrhenoblastoma.<sup>17</sup> This tumor masculinizes its host but does not cause hypertension, diabetes, polycythemia, purplish striations or plethoric obesity. In fact, the symptoms which do occur are precisely those which one would expect and following the prolonged administration of large doses of testosterone propionate to women or eunuchoid men.

*Urinary Hormonal Substances.*—At first thought it might be inferred that the probable origin of adrenal-like ovarian tumors might be determined by chemical analyses or bio-assay of the urine for hormonal or hormonal-like substances. Here also one encounters difficulties, because in cases of proved adrenal cortical tumors a variety of these substances have been found in the urine by various workers at various times. Among these are estrogenic substances, androgenic substances, substances which are said to prolong the lives of adrenalectomized animals, 17-ketosteroids and inactive compounds which are related chemically to the hormonal ketosteroids.

If one accepts the validity of these conflicting observations, the only permissible conclusion is that histologically similar adrenal cortical tumors have differing functional capacities. The variation in the clinical pictures lends weight to this view. At present, the tendency is to emphasize the significance of the presence of excessive quantities of 17-ketosteroid material in the urine. From our own experience with a number of unreported cases of proved adrenal cortical tumor, we have reason to believe that the excessive excretion of these compounds is not necessarily a concomitant of adrenal cortical tumor, and, furthermore, that when these compounds are excreted, the values obtained do not by any means parallel the intensity of the clinical picture. When we turn to the ovarian counterparts we again find the same type of variability but less easily demonstrated because of the limited number of observations. To exemplify; in the case reported by Saphir and Parker (case 5), an unusually high titer of urinary estrogens was obtained. In contrast, in most of the other cases in which this determination was made, the values were normal or subnormal. In the case that we have reported, the excretion of estrogens was within normal limits, but the excretion of 17-ketosteroids was definitely excessive.\* This observation

\*A large amount of urine was obtained for study of the particular ketosteroids that were responsible for the high qualitative values that were obtained. Unfortunately, through a technical error in extracting the urine the results were completely vitiated except for the extraction of a few milligrams of androsterone which is without significance. It is well to bear in mind that the colorimetric reaction on which the determination of the 17-ketosteroids is based is a group reaction which is not specific for any one substance.

further supports the view that the functional behavior of the tumor was compatible with that of a tumor of the adrenal cortex; however, it does not necessarily exclude other possibilities.

### Summary

Like arrhenoblastomas, the adrenal-like ovarian tumors tend to masculinize their hosts but the tendency toward the production of a bizarre type of fat distribution, the occurrence of purplish striae, arterial hypertension, polycythemia and so forth, relate them more closely to adrenal cortical carcinomas from a functioning standpoint. Histologically, the tumors do not appear to arise through luteinization of pre-existing granulosa-cell neoplasms and an origin from adrenal cortical rests seems more logical than does a derivation from corpora lutea. An origin by way of teratomatous development likewise remains unproved. Some of the tumors appear to be cytologically malignant and in one instance death resulted from metastasis.

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## ADRENAL REST TUMOR OF THE OVARY

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**A**DRENAL rest tumors of the ovary are a form of tumor frequently, but not invariably, associated with defeminization and masculinization of the female.

The scientific literature contains very few reports of such a type of tumor, and much confusion exists insofar as the histogenesis and pathology of the tumor are concerned.

In 1939, Van Kirk and Edwards<sup>1</sup> could collect only 27 such cases, some of which were not positively identified as primary in the ovary. Peham<sup>2</sup> is accredited with having reported the first case in 1899.

Rottino and McGrath,<sup>3</sup> later in 1939, reported that only seven cases recorded previously in the literature could be accepted as being of true adrenal rest origin; and they summarized these seven cases, adding two additional cases of their own finding. They accredited Bovin<sup>4</sup> with having reported, in 1908, the first adrenal rest tumor of the ovary.

Most authors agree that the adrenal rest tumor of the ovary arises from misplaced cell inclusions of the adrenal cortex or from mesenchymal cells in the ovary destined to produce adrenal cortex, rather than from lutein cells. That such rests do occur was shown by Marchand,<sup>5</sup> who, as early as 1883, demonstrated accessory nodules of suprarenal gland tissues in the broad ligaments.

Embryologically, the ovaries, testes, and adrenal cortex have a common origin, being derived from the coelomic epithelium of the urogenital fold. This urogenital fold in later embryonic life divides to form the adrenal cortex and the gonads. It is not without possibility, therefore, that misplacement of cells occasionally occurs in the ovary from the neighboring adrenal *anlage*. Schiller,<sup>6</sup> after careful histopathologic study, demonstrated adrenal rests in 20 per cent of infants' ovaries. Novak<sup>7</sup> states that aberrant adrenal rest tissue is not infrequently seen, especially along the course of ovarian or spermatie vessels. He adds that adrenal rests are rare in the ovary, but have been noted in the cortex, hilum, and near cysts. Other adrenal rests have been reported in the broad ligament, ovarian ligaments, uterus, inguinal canal, epididymis, and even in the liver near the adrenal gland.<sup>8-10</sup>

The mere presence of adrenal tissue in an aberrant site does not necessarily mean that the clinical signs of masculinization will always be present. The tendency for aberrant adrenal tissue to become neoplastic cannot be doubted, however.



Objections to adrenal rest tumors being primary in the ovary have been voiced by some investigators, who believe that such tumors develop from accessory adrenal cell inclusions which are present only in the broad ligament.

Glynn<sup>9</sup> denies even the existence of adrenal rest tumors and states that all such tumors thus classified are of lutein origin. Novak admits that luteomas do exist, but believes that the vast majority of these tumors are of an adrenal rather than of a lutein origin. Schiller accepted only 3 cases from the literature as being examples of ovarian luteomas.

Because of the confusion which exists in the histopathology of adrenal rest tumors, they have been reported in the literature under varying classifications and an adequate survey of the literature is thereby almost impossible. The tumor has been variously referred to as primary hypernephroma of the ovary, hypernephroid tumor of the ovary, interrenaloma of the ovary, cortical adrenal tumor of the ovary, adrenal rest tumor of the ovary, and luteoma. In 1939, Rottino and McGrath suggested the term "masculinovoblastoma" as a name being descriptive of its biologic properties and to differentiate the tumor from arrhenoblastoma.

From the recorded cases, no correlation appears to exist between the age of the patient and the occurrence of the tumor. The tumor has been observed at various ages from 3 to 65.

Stadium<sup>11</sup> suggested that inasmuch as no case had ever been reported in a colored patient, this might be taken as a diagnostic hint. The majority of case reports, however, have come from European clinics where the Negro population is small. Our case refutes this hypothesis.

The tumor is generally unilateral, varying in size from several millimeters to 3 or 4 centimeters, occasionally slightly larger. It is most often noted in the hilar region of the ovary, although it may involve the whole ovary by contiguity. It is a solid tumor, often encapsulated, rarely becoming cystic, occasionally showing small areas of hemorrhage and necrosis on cut surface. The external surface is usually smooth. The tumor is generally of soft consistency, and has a characteristic yellow color, resembling closely its analogue, the adrenal.

Microscopically, the tumor is composed of numerous, conspicuously arranged, cords of cells or acini, separated by fibrous trabeculae, and composed of large, acidophilic cells having an abundant granular or spongy cytoplasm and a relatively large, round or slightly indented, dark staining, centrally placed nucleus. The cells are round, or more commonly, roundly polygonal. The cell outline is well defined, and the surface where the adjacent cells meet is usually flattened. The nuclear nucleoli are very prominent. Delicate capillaries and equally delicate connective tissue strands can be noted coursing through the acini. The

arrangement of cells often suggests that of the zona fasciculata or even the zona glomerulosa of the adrenal cortex.

Greenhill, Greenblatt, and Brown<sup>12</sup> reported in 1939 that adrenal cortical adenomas and adrenal rest tumors of the ovary presented not only comparative morphologic features and staining reactions, but also identical polariscope characteristics. This may serve as a basis for differential diagnosis from the luteoma with which the adrenal rest tumor of the ovary may be confused.

Hormone assay tests may also be of value in the differential diagnosis.<sup>13</sup> With adrenal rest tumors, a high level of estrin can be detected in the urine; whereas with the luteomas, corpus luteum hormone is found.<sup>14</sup>

Downes and Knox<sup>15</sup> demonstrated microchemically that the cells of adrenal rest tumors of the ovary contain lipids and glycogen. Ewing<sup>16</sup> states that glycogen occurs in the cells of embryonic tumors, and is especially abundant in the cells of hypernephroma, chorioma, and teratoma. Chemical analysis shows also the presence of phospholipids and cholesterol.

The androgenic substance or substances secreted by the adrenal rest cells produce a syndrome in the female of defeminization and masculinization, identical with that syndrome produced by the arrhenoblastoma. There is an amenorrhea coming on rather suddenly after previously regular menstrual periods, associated with a regression in the size of the breasts among older patients or arrested development in younger patients. Hirsutism appears, with the development of a chin and upper lip beard, a masculine pubic escutcheon, and the growth of coarse hair on the chest and extremities. Baldness results from a falling out of the hair over the head, while acne of the face and upper part of the trunk may sometimes be a prominent sign. There is a redistribution of the subcutaneous tissue, such that the body takes on a masculine appearance. Broadening of the shoulders and an increase in the firmness of the skeletal musculature are noted. The voice becomes deepened and more resonant as a result of hypertrophic laryngitis. Hypertrophy of the clitoris may be excessive, and there is frequently a loss of libido. Infertility, or sterility, may also be encountered.

It is probable that most of these tumors are benign, as is true of comparable lesions of the adrenal. Excision of the tumor frequently produces moderate to complete regression of all signs and symptoms. The voice changes, however, usually are permanent. If the hirsutism does not disappear postoperatively, the presence of additional adrenal cortical tissue in other aberrant locations is a possibility.

It is interesting to note that the sex hormone produced by the adrenal rest cells produces sex characteristics and changes not of the same but of the opposite sex.<sup>17</sup> In the male, the adrenal rest tumor is known to produce a female type of adiposity, breast hypertrophy, at times with lactation; testicular atrophy, and loss of libido. Schiller has

recorded two such instances of feminization associated with adrenal-like structures in the testicle. In children, the tumors bring about a precocious puberty.

The following case, which came under observation at Kings County Hospital in 1937, presents a clinical course and gross and microscopic findings typical of an adrenal rest tumor of the ovary.

### Case Report

The patient, a 29-year-old Negro housewife, presented herself for admission to Kings County Hospital on October 21, 1937. Her chief complaint was that she had not menstruated for the previous four years.

The patient first menstruated at the age of 12, the menses recurring regularly thereafter at 28-day intervals, lasting 3 to 5 days. In 1933, the menses had suddenly ceased and had never recurred. Concurrently, the patient developed a dull ache in the left lower quadrant which radiated to the lumbar region of the back. The ache was persistent, and at times became quite severe. In 1934, the patient first noticed her voice becoming deeper in pitch. She first noticed a beard developing in 1935.

Past medical history was noncontributory. She denied venereal disease. She had had no previous operations or serious illnesses. She had never been pregnant.

Physical examination revealed a well-developed and well-nourished colored female. The voice was deep. The face was covered with a thick beard, which was especially marked on the upper lip. The hair of the body was masculine in character, the abdomen and back being covered by a considerable amount of small coarse hair. A masculine escutcheon was present. Lungs were clear to percussion and auscultation. Heart was not enlarged. Blood pressure was 120/70. The abdomen was obese, soft, not tender, and no abnormal masses were palpable.

Pelvic examination revealed a clitoris 4 or 5 times the normal size, the glans measuring 5 centimeters in length and  $1\frac{1}{2}$  centimeters in diameter at its base. The labia were not abnormal. The cervix was nulliparous, freely movable, and faced anteriorly. The uterus was firm, retrocessed, but freely movable. In the right fornix a nontender, somewhat nodular mass, the size of a small orange, was palpated. The left fornix and posterior cul-de-sac were clear.

The urinalysis was negative. Blood Wassermann was negative. Blood urea was 20 mg. per cent; creatinin 1.18 mg. per cent; sugar 88 mg. per cent. The white cells numbered 8,800 with 72 per cent polymorphonuclear leucocytes. The red cells numbered 4.3 million, and the hemoglobin was 80 per cent.

A roentgenogram of the abdomen showed no evidence of any mass displacing the intestinal tract. Retrograde pyelograms showed both kidneys to be normal in size and position, and no calculi were noted.

A preoperative diagnosis of arrhenoblastoma of the right ovary was established, and patient was prepared for operation.

On October 27, 1937, an exploratory laparotomy was performed through a suprapubic midline incision. The peritoneal cavity contained a small amount of clear fluid. The right ovary was the site of a hard tumor, the size of an orange, which was diffusely firm and showed no evidence of cystic degeneration. The tumor was attached by a wide

base which spread medially into the broad ligament. The tumor lay free, was not otherwise adherent to any viscera, and was freely movable. The right tube was intimately attached to the tumor along its entire length. Large varicosities were noted in the right broad ligament. The left tube and ovary appeared normal. The uterus was hypoplastic, but of the usual color and consistency, and freely movable. Both kidneys were palpated and felt to be of usual size. The adrenal glands were not palpable, and no abnormal masses were noted.

A right salpingo-oophorectomy was performed.

The postoperative course was uneventful. The patient was discharged to the outpatient department on the sixteenth post-operative day.



Fig. 1.—Low-power photomicrograph, showing the relationship of the adrenal tumor with the ovarian stroma.

#### *Pathologic Report.*—

The specimen consisted of a large, firm, somewhat nodular, tumor mass, measuring 7 by 5 by 3 centimeters. The capsule was grayish-white in color, was smooth externally, measured 1 to 2 millimeters in thickness on section. The tumor consisted of solid yellow tissue, arranged in alveolar formation, with intervening bands of gray fibrous tissue similar to that of the capsule. The alveolae were concentrically arranged about a small grayish center. The Fallopian tube appeared somewhat thickened, but showed no other gross changes.

Microscopically, all sections from various portions of the tumor revealed essentially the same architecture and consisted of diffuse palisaded sheets of moderate-sized round and polygonal cells having considerable amounts of acidophilic, spongy cytoplasm and small deeply-staining nuclei. The cells were arranged in acini and were supported by a delicate, vascular stroma, the cell borders being well-demarcated.

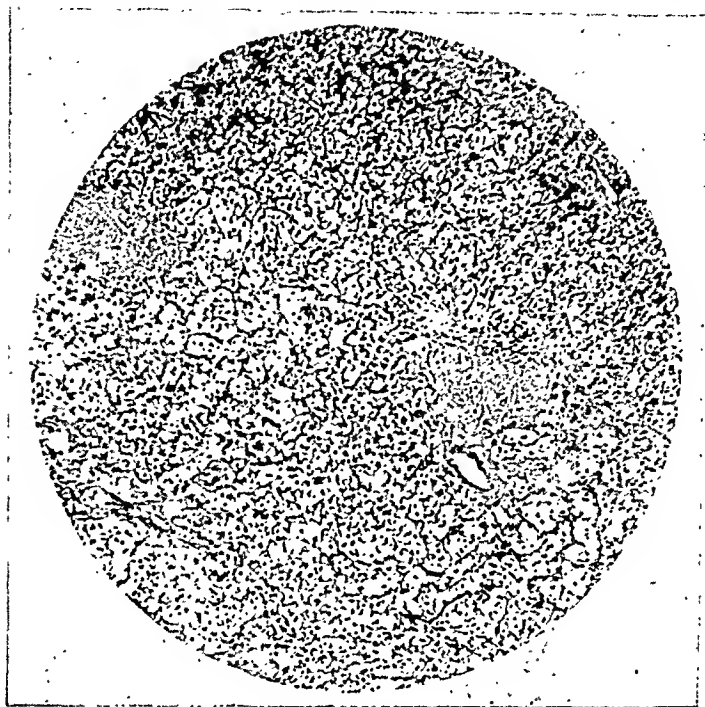


Fig. 2.—Low-power photomicrograph, showing the tumor divided by large fibrous septa into alveolar masses of diffusely palisaded cells closely resembling those of the adrenal cortex.

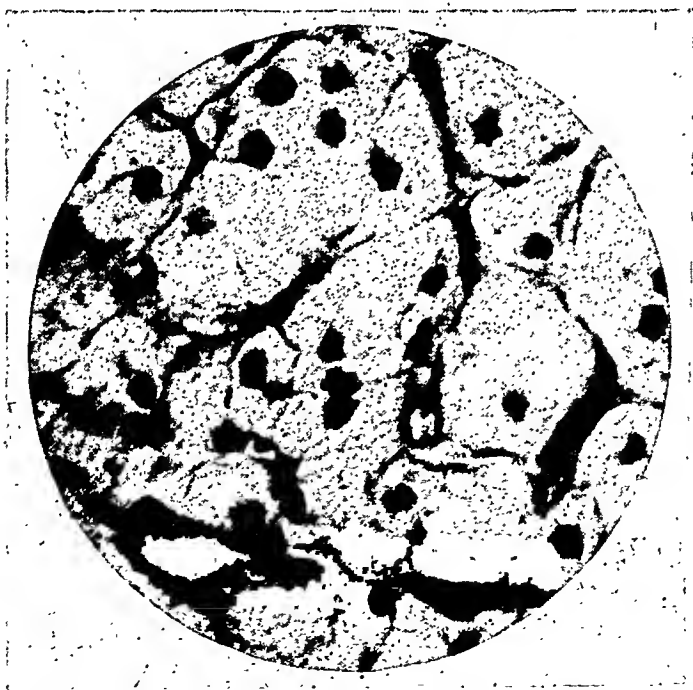


Fig. 3.—High-power photomicrograph, showing the large, well-defined, polygonal cells with abundant granular cytoplasm and round, deeply staining nuclei.

Large fibrous septa extended through the tumor and divided it into large alveolar masses. The cellular arrangement closely resembled that of normal adrenal cortex. Cross section of the Fallopian tube showed a chronic salpingitis.

The histopathological diagnosis was adrenal rest tumor of the ovary.

The patient subsequently returned to the outpatient department, six months postoperatively. At this time, she was again menstruating normally, the periods recurring regularly every 28 days and lasting 4 days. The hair on the face, abdomen, and chest was falling out and was noticeably diminished in amount and texture. Patient was last heard from on February 18, 1941, at which time she was applying for work as a domestic worker and was enjoying good health at that time. Recent efforts to locate the patient have been unsuccessful.

### Summary

A case of adrenal rest tumor of the ovary, occurring in a colored female and associated with marked changes of defeminization and masculinization, is presented. Surgical removal of the tumor produced regression of most of the signs and symptoms. The patient, when last heard from, over three years after operation, was enjoying good health.

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855 OCEAN AVENUE

451 CLARKSON AVENUE

## INTRAVENOUS AMINO ACIDS IN NEPHROTIC TOXEMIA OF PREGNANCY\*

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IT IS generally acknowledged that the pregnant woman requires about 15 per cent more calories, 25 to 50 per cent more iron, 20 to 25 per cent more vitamins, and 30 to 45 per cent more protein than does the normal nonpregnant woman. Unless the proper selection of foods is made, her diet will result in too great an increase in weight but will at the same time be deficient in iron, proteins, and possibly vitamins. The woman who eats less during pregnancy than before almost surely will develop a deficiency. This is substantiated by the reports of Strauss,<sup>1, 2</sup> Tompkins,<sup>3</sup> and Arnell, et al.,<sup>4, 5</sup> which indicate that a protein deficiency edema is common during pregnancy. The high incidence of vitamin deficiencies and anemia in pregnancy is also well established.

The relationship of nutritional deficiencies to toxemias of pregnancy is sufficiently close to suggest to some observers, e.g., Ross,<sup>6</sup> Tompkins,<sup>3</sup> and Bibb,<sup>7</sup> that a nutritional deficiency may be a causative factor.

Certainly in pregnancy the physician should attempt to prevent the development of a nutritional deficiency as well as to correct any deficiency that already exists. This seems to be of particular importance in the patient with a toxemia. It is of interest that the microscopic evidence of liver damage in toxemias of pregnancy closely resembles that seen in livers injured by toxic agents such as chloroform and cinchophen. The importance of dietary protein as well as carbohydrate in protecting the liver against these toxins was noted by Davis and Whipple,<sup>8</sup> and has recently been given prominence by Ravdin,<sup>9</sup> Miller and Whipple,<sup>10</sup> Messinger and Hawkins,<sup>11</sup> and others.

The following report illustrates the important role played by nutritional therapy in a case of nephrotic toxemia of pregnancy.

Mrs. M. O'C., a graduate nurse, aged 22 years, was seen first at home on January 15, 1942, when she was approximately sixteen weeks pregnant. Her chief complaint was marked dyspnea, generalized edema, and weakness.

Her last menstrual period had occurred on September 3, 1941, and her expected date of confinement was June 10, 1942. Her illness began about December 1, 1941, when she was about two and a half months

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pregnant and under the care of her family physician. At that time she noticed increasing pallor, dyspnea on exertion, and swelling of the extremities. About December 25, 1941, edema was general, but it was marked over the buttocks and the extremities. Headache was constant. Treated with magnesium sulfate daily, Mrs. O'C. showed markedly decreased edema, and the headaches became less severe. On January 10, 1942, the edema increased, the headache became continuous, the pallor was marked, and dyspnea was worse, especially on exertion. A productive cough developed, and the sputum was occasionally blood streaked.

The patient gave a history of tonsillectomy and appendectomy in 1929, streptococcal sore throats in 1937 with no kidney nor heart complications that she was aware of, and rheumatic fever (six weeks in bed) in 1940.

On January 15, 1942, physical examination revealed marked pallor, a reddened injected pharynx, and a temperature of 100° F. The blood pressure was 178/112. The eye fundi were normal. The heart rate was 116 per minute, and the sounds irregular and of fair quality. Percussion revealed normal cardiac dullness. Presystolic and systolic murmurs were heard at the mitral area. Moist râles were heard in both lung bases with no areas of dullness in percussion. The liver edge was palpable and tender. A poorly-healed, right rectus sear was present. The uterus was enlarged to the level of a sixteen weeks' pregnancy. The urine gave a four-plus reaction for albumin, and showed 5 to 10 red blood cells, 20 to 30 white blood cells, and 3 to 4 hyaline casts to the high power field. Weight was 132 pounds, having increased 24 pounds since the onset of pregnancy, and edema was generalized.

A tentative diagnosis was made of rheumatic heart disease class III, streptococcal infection of the throat, and subacute glomerulonephritis complicating pregnancy of sixteen weeks' duration. Although the patient was referred for hospitalization, she remained at home. However, since throat irrigations and rest in bed produced no noticeable improvement in her condition, she was admitted to St. Vincent's Hospital, January 17, 1942.

Family history was negative. The history obtained from the training school confirmed the fact that she had had streptococcal sore throats in 1937. During the three years of training, urine analyses at three-month intervals had been negative. Blood chemistry examinations had been normal, and chest x-rays negative except that "the right hilus and left upper hilus show areas of calcified deposits suggestive of healed juvenile tuberculosis. The right diaphragm is irregularly raised due to adhesions, but there is no sign of active tuberculosis at this time." Her blood counts had been normal in every respect.

Following graduation from training school, the patient had rheumatic fever in September, 1940, and was confined to her home for six weeks. No laboratory data were available for this period. A report on chest x-rays taken in November, 1940 states "heart measures 12 plus cm. in the transverse axis. There is, however, a straightening of the left cardiac border which is frequently an early sign of mitral pathology. There is no evidence of recent lung parenchymal infiltration or pleural involvement." A clinical examination was made two months later (January 4, 1941), as follows: "Presystolic and systolic murmurs heard at the apex in the recumbent position. Left lateral prone position accentuates the presystolic murmur. The heart is not enlarged, rhythm is regular, and the rate is 72 per minute."



*Diagnosis.*—"Rheumatic heart disease. Mitral stenosis and mitral insufficiency Class I. Color poor. Patient is below normal weight, 102 pounds. Urine negative for albumin with negative microscopic examination." The electrocardiogram revealed at that time "right axis deviation and broad and bifid P-waves."

From the history given above it is evident that the attack of rheumatic fever had impaired the patient's heart valves to some degree, but at that time there was no evidence of involvement of the kidneys.

The patient was married in January, 1941, at the age of 21. She became pregnant and had a spontaneous abortion in April of that year when she was six weeks pregnant. Her history was then negative until her last period, September 3, 1941. Her progress up to admission to the hospital, January 17, 1942, has been given.

Upon entering the hospital the patient appeared acutely ill. Edema and pallor were marked, blood pressure was 144/96, temperature was normal. Presystolic and systolic murmurs could be heard at the mitral area, the liver edge was not palpable or tender, and the lung bases were clear. A catheterized specimen of urine gave a four-plus reaction for albumin. The specific gravity was 1.026. Microscopic examination of the urine showed 5 to 8 red blood cells, 20 to 25 white blood cells, and no casts per high power field.

Blood examination showed sedimentation time 26 minutes to 18 mm., 35 minutes to 26 mm.; hemoglobin 62 per cent; red blood count 2,600,000; white blood count 6,800 with differential count normal; Kahn test negative. The blood was type O.

On January 18, 1942, the urea clearance was 35 c.c. (100 per cent normal function). Chemical studies of the blood showed the following:

		NORMAL
Sugar	83	75 to 120
Uric acid	2.3	2 to 4
Urea N	11	10 to 20
Creatinine	1.5	1 to 1.5
Chlorides	554	380
Cholesterol	417	150 to 250
Albumin	0.96	3.8 to 6.0
Globulin	1.86	1.5 to 3.0
Total protein	2.82	6.3 to 8.0

The twenty-four-hour specimen of urine consisted of 880 c.c. (intake 1,000 c.c.) and contained albumin 11.5 Gm., with 10 to 15 red blood cells, 30 to 40 white blood cells, and occasional hyaline and granular casts per high power field.

Eye examination January 19, 1942, revealed the media clear, vessels A:V ratio 2:3. There was no exudate or hemorrhage.

The cardiologist reported as follows: "Patient is lying flat in bed with no respiratory distress. Vessels of the neck are not remarkable; thyroid isthmus is palpable. Heart by percussion normally situated; left border within normal limits. There is no thrill, heart sounds are of good quality. There is no notable accentuation of any of the base sounds. Over the pulmonic area there is a blowing systolic murmur. Rhythm is regular, rate 90, which slows markedly on vagus nerve stimulation. Edema of the face previously reported is not present now. Edema of the lower extremities and presacral area is marked. Impression: The subjective symptoms and signs are not due to cardiac failure. The physical examination does not reveal signs of chronic valvular disease. Electrocardiogram: Sinus arrhythmia."

TABLE I. INTRAVENOUS AMINO ACIDS IN NEPHROTIC TOXEMIA OF PREGNANCY

DATE	INFUSIONS	DIET (C 300, F 50)	AVERAGE TOTAL PROTEIN PER DAY	PLASMA PROTEIN GM./100 C.C.	HGB.	R.B.C.
Jan. 19 to Mar. 24	2,750 c.c. plasma 2,800 c.c. whole blood	P 160	165†	2.45 to 3.9	10.8 (62%)	3.01
Mar. 25 to May 3	45 Gm. amino acids/day*	P 100	145	3.8 to 4.8		
May 4, 5, 7, 8	90 Gm. amino acids/day	P 100	190	4.4 to 4.2	11.6 (68%)	3.36
May 6	400 c.c. whole blood	P 100	115†	4.4		
May 9 (Opera- tion)	45 Gm. amino acids			4.1		
May 10 to 21	45 Gm. amino acids/day	P 100	145	4.8		
May 23 (Dis- charged)	650 c.c. whole blood	P 100	125†	4.8	11.3 (66%)	3.0
Oct. 13				6.44	14.3 (84%)	4.0

\*6 days out of 7.

†Plasma calculated to contain 7% protein. Whole blood 54% plasma.

## RENAL FINDINGS

DATE	UREA		ALBUMINURIA QUANT.		URINE C.C./24 HR.	WEIGHT LBS.	
	CLEARANCE	QUAL.	GM./24	HR.			
Jan. 19 to Mar. 24	54 c.c. (100%)	4+	7.5 to 12.5		450 to 1,000	132	increasing to 135
Mar. 25 to May 3		4+	8.3 to 14.2		1,000 to 2,250	135	decreasing to 126
Oct. 13	61 c.c. (110%)	3+	5.9		1,400	112	

On January 20, 1942, x-ray of the chest showed "the heart measures 12½ cm. in the transverse axis. There is an increase, however, in the vertical diameter of the heart and recession of the aortic arch. These changes suggest enlargement of the right ventricle. The hilar densities and pulmonary markings are slightly increased. The apices, extreme peripheries, and lower angles are clear."

The patient was placed on a diet (Table I) consisting of 300 Gm. carbohydrate, 160 Gm. protein, and 50 Gm. fat. Vitamin, calcium and iron therapy was instituted, and vitamin C, 2 c.c. parenterally, was administered daily. The patient was extremely cooperative, and took her food *in toto* despite the fact that many times this required a great deal of effort.

On January 19, 1942, the patient was given a whole blood transfusion of 500 c.c. by the direct method. Another 500 c.c. whole blood transfusion was given on February 5, 250 c.c. on February 9, and 400 c.c. on February 12. Plasma transfusions (250 c.c.) were given on January 24, 27, and 29, and on February 3, 6, 9, 12, 18, 20, 24 and 28. After the first whole blood transfusion (January 19), the blood protein increased from 2.82 to 3.95, which was the highest point reached in spite of the high-protein diet, the 2,750 c.c. of plasma, and the 1,650 c.c. of whole blood given up to March 10.

The hemoglobin and red cell count steadily decreased, and on March 11, 13, and 17 a total of 1,150 c.c. of whole blood was given. This brought the total transfusions up to 2,800 c.c. of whole blood and 2,750 c.c. of plasma. No untoward reactions had been noted at any time from either the plasma or the whole blood transfusions.

The last three blood transfusions had brought the patient's total serum protein to 3.9 Gm. per 100 c.c. of blood. After rest in bed and the transfusions, the râles in the lung bases cleared, and the blood pressure dropped, varying between 130/70 and 106/64 during the patient's stay in the hospital. The edema was, however, still very marked especially in the dependent portions of her body. The total serum proteins fluctuated widely, and no real improvement could be noted in the patient's condition except for some slight improvement in the blood picture. There was still a good deal of doubt whether either she or the baby could survive.

On March 25, because of the patient's distaste for protein, her diet was changed. The carbohydrate and fat intake remained the same (C 300, F 50), but the protein was decreased from 160 to 100 Gm. per twenty-four hours and administration of amino acids solution was begun. Three hundred c.c. of 15 per cent amino acids solution (45 Gm. amino acids) were given every day from March 25 to April 29, inclusive, except on April 7, 13, 17, and 26. For the first three days the amino acids were given by mouth; thereafter they were administered intravenously. On April 30, after receiving 250 c.c. of amino acids solution, the patient experienced a moderately severe reaction, with chill, nausea, and epigastric pain. The intravenous solution was immediately stopped and none was given on May 1. Three hundred c.c. was given again on May 2 and 3, 600 c.c. on May 4, 5, 7, and 8, and 300 c.c. on the morning of the operation, May 9. Four hundred c.c. of whole blood was given on May 6 to combat the slight anemia.

After the administration of the amino acids was started, the serum proteins increased from 3.9 to a high of 4.8, then decreased to 4.4 and remained at that level, or slightly lower, until after her delivery by cesarean section, May 9, when the level rose to 4.8 Gm. per 100 c.c. of blood.

Clinically there was marked improvement after the amino acids were begun. The patient became more interested in her surroundings and very enthusiastic and cooperative. The edema, which had shown no noticeable change during the plasma and blood transfusions, decreased about forty per cent during the amino acids regime, and cleared entirely by the sixth day following delivery of the baby, except for slight ankle edema.

The daily urine analysis consistently showed a four-plus reaction for albumin. The red blood cells observed per high power field varied from 2 to 50, white blood cells from 10 to 100, and casts of the hyaline, granular, and cellular type were occasionally seen. A bi-weekly twenty-four-hour specimen showed 11 to 14 Gm. of protein per liter.

During the plasma and blood transfusions, fluid output varied between 500 and 900 c.c. per twenty-four hours, except on March 12, 14 and 18, when it was 1,160, 1,140, 1,100 c.c. on the three consecutive days following the whole blood transfusions. There was no noticeable increase in output following the plasma. Upon administration of the intravenous amino acids, the output was increased to a low of 1,680 c.c. and a high of 2,630 c.c. per twenty-four hours. On the days when the amino acids

were not given, the output varied between 585 c.c. and 860 c.c. per twenty-four hours.

On admission the patient weighed 132 pounds, a gain of 24 pounds since the onset of pregnancy. During the plasma and blood transfusion period her weight increased to 135 pounds, then decreased to 131 pounds. After the amino acids were begun, her weight decreased 5 pounds, so that on the day of operation the patient weighed 126 pounds.

Examination revealed the baby in transverse axis with the head on the left side and the face directed downward, with the cervix long, thick, and pointing high, forward, and toward the symphysis. Clinically the patient's pelvis showed a slight android tendency at the inlet but there was a satisfactory sacrospinous notch and an average subpubic arch. X-ray confirmed these findings. The anteroposterior diameter of the inlet was calculated to be 9 cm. and the transverse diameter at the spines, 9.5 cm.

The findings given above were considered sufficient to warrant cesarean section rather than an attempt at induction from below. Accordingly, delivery was effected by low-flap section on May 9, 1942, under cyclopropane and oxygen anesthesia, the baby weighing 4 pounds, 15 ounces.

Convalescence was normal, with primary union of the wound. Forty-five Gm. of amino acids were given intravenously daily from May 10 through May 21. On May 23, when the patient was discharged from the hospital, she received 650 c.c. of whole blood. The baby was discharged on the twenty-eighth day after delivery, weighing 7 pounds, 5 ounces.

The patient was followed at monthly intervals after discharge. She seemed well, and was carrying on regular housework and caring for her baby. Monthly urine analyses gave a two- to three-plus reaction for albumin. Two twenty-four-hour specimens revealed 5 to 6 Gm. of protein per liter of urine.

On October 13, 1942, five months after delivery, the patient returned to the hospital for checkup. The values reported for chemical studies of the blood were as follows:

		NORMAL
Sugar	84	75 to 120
Uric acid	3	2 to 4
Urea N	9	10 to 20
Creatinine	1.2	1 to 1.5
Chlorides	515	380
Cholesterol	295	150 to 250
Albumin	3.71	3.8 to 6.0
Globulin	2.71	1.5 to 3.0
Total protein	6.44	6.3 to 8.0

Urea clearance was normal (110 per cent), but the urine still showed a high daily output of protein (5.9 Gm. per liter). The diet had been maintained at a high-protein level and included 45 grams of amino acids by mouth three times a week.

### Discussion

Observation of the values reported for chemical studies of the blood upon admission of the patient shows that the blood sugar, uric acid and urea nitrogen are low-normal, probably an indication of a deficient diet, a failure to utilize ingested foods, or both. The creatinine is high-normal, but the cholesterol is markedly increased because of faulty metab-

olism. It can be seen that the albumin and globulin are decreased to a dangerous level. The protein loss through the urine has all but depleted the plasma albumin and has unbalanced the albumin:globulin ratio. Total protein is severely reduced.

A comparison of the results of chemical analyses of the blood upon admission with those reported five months after delivery, October 13, 1942, seems to point to improved nutrition due to supervision of the diet. The cholesterol, while still above normal, is markedly improved, as are also the albumin and globulin values.

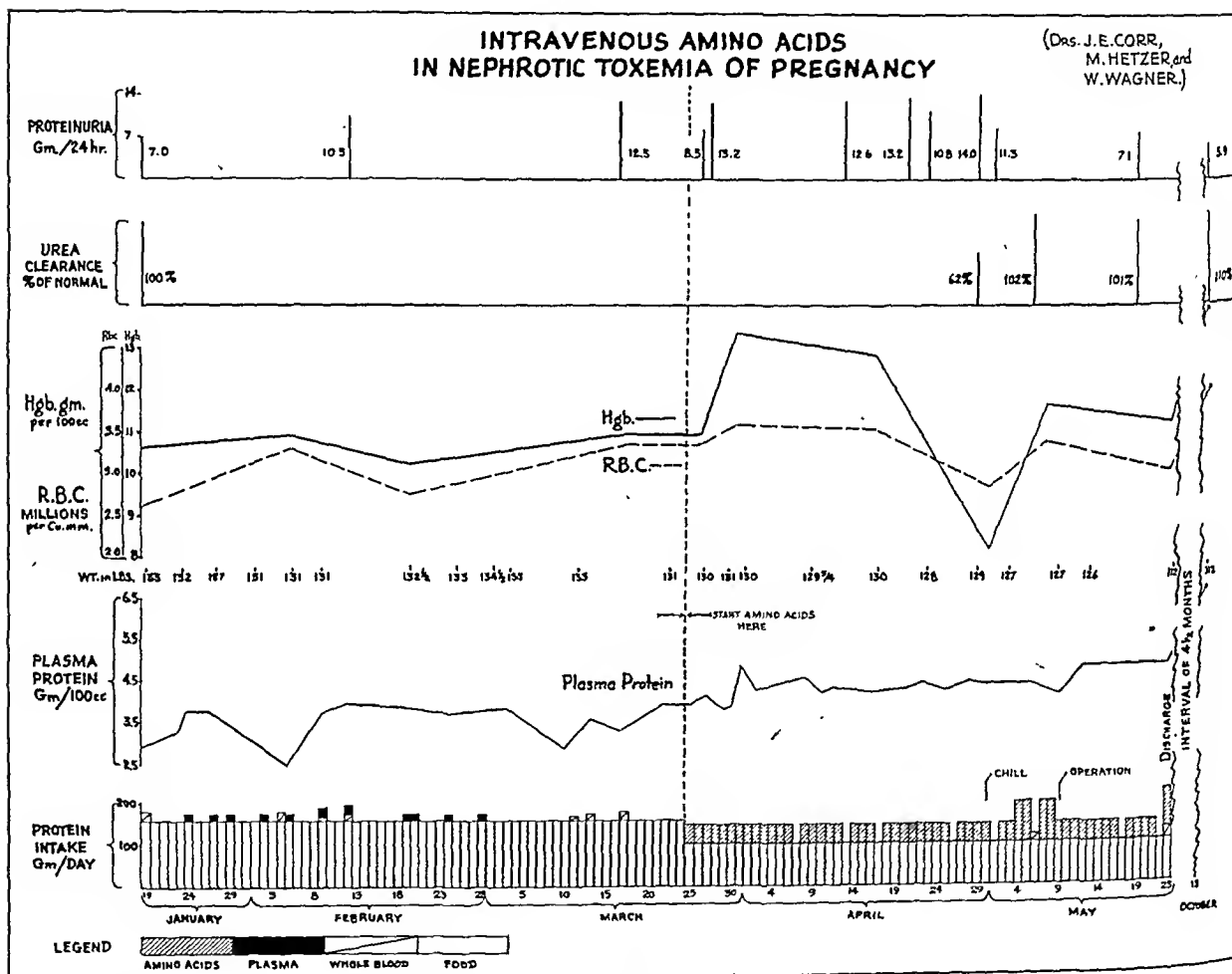


Fig. 1.

The graph (Fig. 1) divides itself very conveniently into two two-month periods, the first, from the date of admission January 17 to March 24; the second, from March 25 to the date of discharge, May 23, 1942. Each period represents a different form of therapy and a variation in the diet. Reading this graph from below upward, we note that the figures represent the daily protein intake, the plasma protein concentration, the patient's weight, the red blood cell count, the hemoglobin in grams, the urea clearance, and the proteinuria in grams per liter.

Plasma and whole blood have been converted to protein in grams on the basis that 7 per cent of plasma is protein and 54 per cent of whole blood is plasma. No allowance is made for the protein content of the red blood cells, for it has been repeatedly shown that they are not metabolized as protein when injected by vein. During this first period, when the basic diet contained 160 Gm. of protein daily, the protein derived from the transfusion of 2,750 c.c. of plasma and 2,800 c.c. of whole blood improved the protein intake to an insignificant degree. It produced a wide fluctuation of the plasma protein level and did not cause any sustained increase. This was doubtless due to the irregularity with which the whole blood was given, since the patient had to depend upon relatives and friends for procuring the blood.

In the same period it is seen that the weight decreased from 132 to 131 pounds. This represents a weight loss of one pound, but if we consider that in this period of two months the patient should have gained about five pounds in the normal course of her pregnancy, it is fair to assume that an actual loss of 6 pounds occurred which can be attributed to an extracellular fluid loss.

As this pregnancy advanced, the red blood cell count and hemoglobin estimation showed little change, the urea clearance varied slightly, and the proteinuria increased from 7 Gm. to 12.5 Gm. per twenty-four-hour urinary output.

The second period represents the amino acid regime. At this point, the patient began to tire of the high-protein diet, which was, therefore, reduced from 160 Gm. to 100 Gm. of protein daily, the grams of carbohydrate and fat remaining the same. To this diet was added 45 Gm. of amino acids daily. There occurred a dramatic increase in the red blood cell count. It is to be remembered that the patient had had iron therapy throughout her entire stay in the hospital. It is possible that at this point she formed an increased amount of hemoglobin because of the availability of globin derived from the amino acids, and, since the patient must have had adequate iron available, the iron may not have been the limiting factor. It is now believed that we do occasionally see protein deficiency anemias. These are, however, rare and represent only speculation on our part.

The plasma protein concentration definitely increased from an average of 3.5 to 4.8 Gm. per 100 c.c. of plasma. The postoperative increase is directly in line with the preoperative increase, and if the interval of four and one-half months between the date of discharge (May 23), and the date of readmission to the hospital for a checkup (October 13, 1942), were presented on another graph, the rate of increase in plasma concentration would be seen to be not too different from the rate of increase which occurred during the last two months of pregnancy.

The weight loss during this second period (131 to 126 pounds) is seen to be 5 pounds. Add to this the normal increase of 5 pounds as in the first two-month period, and we see a decrease in weight of 10 pounds.

The urea clearance and the proteinuria in this period show very little change over that of the first two-month period, except for about a week around April 28. At this point there is a marked fall in the hemoglobin and in the red blood cell count, an increase in the red blood cells in the urine, with a temporary decrease in kidney function, and a slower fall in the plasma proteins. We have attributed this to an acute exacerbation of the nephritis at that time. The increased output of albumin in the urine also suggests that the glomerulonephritis is still active.

The follow-up, five months after delivery, leads us to believe that the pregnancy did not aggravate the patient's nephritic condition. Here again we are speculating because of the lack of prepregnancy laboratory data. The continued presence of red blood cells and casts in the urine indicates a progressive nephritis, but would not the same picture present itself even though the patient had never been pregnant?

### Conclusions

It is difficult to draw conclusions from the findings in this single case presentation, but we have been unable to find in the literature any similarly treated instance of pregnancy complicating a case of chronic glomerulonephritis with nephrotic syndrome. A more complete understanding of the chemistry of the body may, in the future, place an entirely different light on our present concept of nephritis. The clinical use of amino acids is apparently a step in this direction, for plasma and whole blood transfusions alone, or in combination with a high-protein diet, may not compensate for the protein loss through the urine in cases of nephritic and/or nephrotic toxemia of pregnancy.

We wish to express our thanks and appreciation to Frederick Stearns and Company of Detroit, Michigan, for their supply of amino acids; to Richard M. Johnson, M.D., for his invaluable help and advice in the treatment of this patient and in the preparation of this paper; and to Mr. Robert Bateman for assistance in the preparation of the graph.

### Addenda

Since this case was reported on March 23, 1943, the patient was again successfully delivered of a living child, July 31, 1943. A brief review of her case seems warranted at this time.

Her diet when discharged in October 1942 after the checkup at the hospital, consisted of 200 Gm. carbohydrate, 100 Gm. protein and 50 Gm. fat with 45 Gm. of amino acids three times per week. Her last menstrual period was on November 15, 1942, with the expected date of confinement August 22, 1943. When seen on January 8, 1943, the patient's diet was reviewed, and a diet approximating 300 Gm. of carbohydrate, 100 Gm. of protein, and 50 Gm. of fat was suggested, and the amino acids were increased to 45 Gm. daily by mouth. The vitamin and iron therapy was slightly increased. The patient's weight was 112 pounds, the red blood cell count 4,240,000, hemoglobin 78 per cent of normal. Examination of the specimen of urine showed two-plus reaction for albumin, occasional hyaline casts, and no red blood cells. The eye grounds were normal. The uterus was slightly enlarged, in normal position, and movable.

The patient was seen at two-week intervals. Bimonthly twenty-four-hour specimens of urine were examined for albumin which revealed 3.7 to 4.2 Gm. The weight increase was gradual—112 pounds to 130 pounds on May 28, 1943. The blood pressure had varied between 112/58 and 122/68. The fetal heart was heard in the left lower quadrant.

At each examination the patient's ankles and calves were measured. Though not too accurate, this was an index of the nutritional edema as the pregnancy progressed.

## ANKLE AND CALF MEASUREMENTS.

Jan. 8, 1943	R.A.* 8 in.	R.C.* 12 in.	L.A.* 8 in.	L.C.* 12½ in.
Feb. 10, 1943	R.A. 8 in.	R.C. 12¼ in.	L.A. 8½ in.	L.C. 12¾ in.
Mar. 9, 1943	R.A. 8½ in.	R.C. 13 in.	L.A. 8½ in.	L.C. 13 in.
April 6, 1943	R.A. 8½ in.	R.C. 12¾ in.	L.A. 8½ in.	L.C. 13 in.
May 3, 1943	R.A. 8 in.	R.C. 12¾ in.	L.A. 8½ in.	L.C. 12¾ in.
May 28, 1943	R.A. 8½ in.	R.C. 13½ in.	L.A. 9 in.	L.C. 13¾ in.
June 25, 1943	R.A. 10½ in.	R.C. 15½ in.	L.A. 10¾ in.	L.C. 16½ in.
July 2, 1943	R.A. 11¼ in.	R.C. 17¼ in.	L.A. 11¼ in.	L.C. 19½ in.
July 14, 1943	R.A. 11 in.	R.C. 16¾ in.	L.A. 11½ in.	L.C. 18¾ in.
July 20, 1943	R.A. 11½ in.	R.C. 17¾ in.	L.A. 11¾ in.	L.C. 19½ in.
July 27, 1943	R.A. 10 in.	R.C. 17 in.	L.A. 10½ in.	L.C. 18 in.
July 30, 1943	R.A. 9½ in.	R.C. 16½ in.	L.A. 10½ in.	L.C. 16¾ in.
Aug. 10, 1943	R.A. 8 in.	R.C. 12 in.	L.A. 8½ in.	L.C. 12½ in.

\*R.A.—Right Ankle. R.C.—Right Calf.

L.A.—Left Ankle. L.C.—Left Calf.

On June 25, the patient's weight had increased to 139 pounds, and edema of the ankles, legs, sacral area and abdominal wall had increased markedly. By July 2, 1943, there was still further increase, and erythema of the palms of the hands was noted. Questioning of the patient resulted in an admission that her diet was not strictly adhered to as in the past and she stated that she had been unable to procure the amino acids solution. She felt well but the marked edema had interfered with activity. The blood pressure was 128/76 and the weight 147 pounds, an increase of 35 pounds since the onset of pregnancy and 17 pounds in the past five weeks (May 28 to July 2, 1943). A twenty-four-hour urine specimen revealed an output of 720 c.c., containing 15.2 Gm. of albumin, with occasional hyaline and finely granular casts, 1 to 2 red blood cells, and 2 to 5 white blood cells per high power field.

The patient was put to bed at home, her diet was reviewed again with her, and the amino acids solution was increased to four bottles (80 grams of amino acids) per day. The output of urine measured every twenty-four hours showed a variation from 1,120 c.c. to 1,960 c.c. up to July 14, 1943.

On July 19, 1943, when the patient was admitted to the hospital, her blood pressure was 138/80; but on the following day it was 110/56, and throughout her stay in the hospital it varied between 108/54 and 118/70. Her weight was 145 pounds, and, although edema was marked, there was no complaint. The fetal heart was in the left side, the fetus lying in transverse position, with the buttocks in the left iliac fossa.

The diet of C 300, P 100, and F 50 was continued but the amino acids were discontinued until the laboratory data were completed, July 23, 1943. On July 20, 1943, the red blood cell count was 3,460,000, hemoglobin 80 per cent of normal—11.6 Gm. Sedimentation time was 72 minutes to 16 mm. with urea clearance 58 per cent of normal. Urea content of urine 17. From July 19 to July 23 the daily urinary output varied from 430 c.c. to 1,140 c.c., and proteinuria from 9.8 to 17.2 Gm. per twenty-four hours, with 1 to 2 red blood cells, 2 to 4 white blood cells, and occasional hyaline and granular casts per high power field. The phenolsulphonphthalein test for the first hour was 200 c.c., 14 per cent; for the second, 250 c.c., 6 per cent.

Chemical studies of the blood and a comparison of the findings on January 18, 1942, when the patient was admitted to the hospital, with those of the date of



postoperative checkup, October 15, 1942, showed the following:

	JAN. 18, 1942	OCT. 15, 1942	JULY 20, 1943	AUG. 4, 1943	AUG. 12, 1943	NORMAL
Sugar	83	84	86	86	-	75 to 120
Uric acid	2.3	3	2.1	3.8	-	2 to 4
Urea N.	11	9	7	7	-	10 to 20
Creatinine	1.5	1.2	1.3	1.1	-	1 to 1.5
Chlorides	554	515	530	514	-	380
Cholesterol	417	295	433	378	-	150 to 250
Albumin	.96	3.71	2.7	2.6	1.93	3.8 to 6.0
Globulin	1.86	2.71	1.4	1.13	2.45	1.5 to 3.0
Total protein	2.82	6.44	4.1	3.73	4.38	6.3 to 8.0

Following collection of the above laboratory data, the diet of C 300, P 100, F 50 was supplemented by six bottles of amino acids (120 Gm. of amino acids) per twenty-four hours. This was continued until the day of discharge, August 11, 1943.

Twenty-four-hour urine specimens were collected twice a week from July 24, 1943, to July 31, 1943 (0.375 per cent to 5.5 Gm. albumin per twenty-four hours—0.345 per cent to 7.7 Gm.). The urinary output varied from 1,410 c.c. to 2,200 c.c. Measurement of the ankles and calves of the legs showed that edema decreased, though the patient was not kept in bed.

On July 31, 1943, a male child weighing 5 pounds, 8 ounces was delivered by low-flap cesarean section under cyclopropane anesthesia. The convalescence was uneventful, with primary union of the wound.

Postoperative urinary output varied between 1,960 c.c. and 2,460 c.c. (albumin 5.4 to 6.7 Gm.) per twenty-four hours. On August 5, 1943, the red blood cell count was 2,550,000, the white blood cell count 10,600, with hemoglobin 58 per cent of normal. Two transfusions of 500 c.c. whole blood each were given with the result that on August 11, 1943, the day of discharge, the patient's red blood cell count was 4,120,000 with hemoglobin 86 per cent of normal. The patient's weight was 114 pounds, and palmar erythema was still marked. The baby was discharged August 26, 1943, weighing 7 pounds, 4 ounces.

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## THE COMPARATIVE VALUE OF ENDOMETRIAL BIOPSIES AND VAGINAL SMEARS\*

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**A**MONG the methods now in vogue for estimating ovarian function and determining the effectiveness of hormonal therapy, two distinct groupings exist:

- (1) The qualitative procedures, comprising the examination of vaginal smears, and the investigation of the endometrial pattern;
- (2) The quantitative procedures, which include the hormonal assays of blood and urine.

The limited laboratory facilities for the latter and the incidental expense preclude the universal employment of hormone determinations for routine clinical and office work. Vaginal smears and endometrial biopsies, on the other hand, can easily be taken, not only for the diagnosis of ovarian failure, but also to determine the occurrence of ovulation. Particularly when sterility of endocrine origin is a problem, a knowledge of whether or not the patient ovulates is of great importance.

This communication is presented with the thought in mind of evaluating the clinical practicability and the advantages and disadvantages of the vaginal smear method, as compared with the study of the endometrial pattern.

### Vaginal Smear Method

Using the morphologic changes occurring in the vaginal secretion as a criterion, Papanicolaou<sup>1</sup> demonstrated cyclic alterations in the vaginal mucus of women which were similar to smear changes, described by Stockard and himself,<sup>2</sup> in guinea pigs. Subsequently, Papanicolaou and Shorr<sup>3</sup> described the applicability of the vaginal smear method to the diagnosis of ovarian function and the objective evaluation of the effects of estrogenic therapy.

A small amount of secretion is obtained from the vagina by using a glass pipette fitted with a suction syringe or having a rubber bulb attached. The vaginal fluid is expressed on a clean slide and *immediately* immersed in a fixative—a mixture of equal parts of ether and 95 per cent ethyl alcohol. Staining of the slides according to one of the methods proposed by various investigators is then followed by a microscopic examination.

Our observations of the changes in the vaginal smears during the various phases of the normal menstrual cycle, on the whole, coincide

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with Rubinstein's description<sup>4</sup> of these alterations, which may be summarized as follows:

1. *Postmenstrual Phase*.—The follicle is commencing to develop, estrogen elaboration is at a low level and thus proliferation of the vaginal mucosa is only beginning. The epithelial cells in the smear exhibit predominantly large round vesicular nuclei and granular cytoplasm. In addition many leucocytes and bacteria as well as some thick mucus are present.

2. *Preovulatory Phase*.—As the immature follicle develops, the first peak of estrogen secretion is reached. Concurrently there is increase in proliferation of the vaginal mucosa which thickens. The superficial cells which at this stage are further away from their basal blood supply show more cornification. The nuclei of the epithelial cells become smaller, stain deeper and are pyknotic, the cytoplasm has lost its granular contents, is clear and the edges are distinctly defined. Bacteria and leucocytes gradually disappear from the picture.

3. *Ovulatory Phase*.—With follicle rupture there is a sudden decrease in estrogen secretion, which often is reflected by the appearance of some red blood cells in the smear. In addition, there is marked desquamation of cornified cells, there are very few leucocytes and bacteria, and there are some cornified cells with folded edges.

4. *Postovulatory Phase*.—This phase is dominated by a rapidly forming corpus luteum. Since both estrogen and progesterone are now secreted, proliferation and secretion of the vaginal epithelium is stimulated. The smears show continued desquamation of cells which are characteristically crumpled and folded together. Several types of epithelial cells are present. Some are completely cornified, the cytoplasm—wrinkled with scalloped edges—is agranular, while the nuclei are small and dense, fragmented or completely absent. Most frequently the nuclei are pyknotic but sometimes they may be vesicular. Other cells show large and oval nuclei with a wrinkled cytoplasm and scalloped edges; their cytoplasm is granular and occasionally vacuolated. This type is supposedly suggestive of progesterone activity. There is a marked influx of leucocytes and bacteria. The mucus remains abundant.

5. *Premenstrual Phase*.—While progesterone elaboration increases, the smears show cells with larger, more vesicular nuclei. There is an abundance of leucocytes, bacteria and mucus. With the regression of the corpus luteum—accompanied by decrease of production of the ovarian hormones—the cells, which proliferated previously under the influence of estrogenic hormone, slough off and fragment. Their nuclei may be vesicular or pyknotic. The cells may be broken into halves with one part containing the nucleus. The cytoplasm may show partial cornification and granular vacuoles may be present. In addition, few red blood cells, many leucocytes and much mucus, many bacteria and much debris are present. The smear as a whole is termed 'dirty.'

6. *Menstrual Phase*.—The smear consists predominantly of blood and mucus. Since follicle stimulation by the anterior lobe of the pituitary begins anew during the bleeding phase of the cycle, the epithelial cells present reflect the earliest phase of follicular development.

Prima facie from the above it becomes clear that it is more difficult to evaluate the cytology of the vaginal secretion during the second half of the cycle.

Referring to Papanicolaou's description of the changes in a typical 28-day cycle, Mack<sup>5</sup> in his most comprehensive review states, "It is obvious, from the bizarre and varied cytologic patterns described, that more than ordinary microscopic skill and experience is necessary to conduct such investigations." Also in regard to Rubinstein's description it can be said that the proper interpretation of the cytologic appearance of the smear "is the province solely of the expert histologist."

The cytologic appearance of smears obtained from patients with estrogenic deficiency is more clear-cut. The atrophic changes characteristic of ovarian failure are readily recognizable, at least, in severe deficiency cases. There is a great number of round cells, which stain deeply, with large nuclei. Many leucocytes and usually bacteria are present and there is a lack of cornified epithelial cells. Symptomatic relief in estrogen deficiency cases produced by administration of follicular hormone is frequently associated with a transformation of the cytologic pattern of the smear to the type which is found during the proliferative phase of the normal menstrual cycle. However, we have also observed cases in which estrogenic therapy produced complete subsidence of clinical symptoms while the vaginal smear still showed a prevalence of atrophy cells. On the other hand, we observed occasionally transformation of the atrophy smear to complete cornification of the cells without correlation of these changes to symptomatic relief. The same observations were noted by Eissfelder<sup>6</sup> who, reporting on a series of more than 200 menopausal patients, states that the "vaginal smears may not always be a reliable index to therapeutic response."

The differential diagnosis between ovulatory and anovulatory bleeding is oftentimes of great importance and a practical technique not involving tissue removal and simpler than the determination of urinary pregnandiol complex as devised by Venning and Browne<sup>7</sup> would be of inestimable value. It has been our experience that the vaginal smear method certainly does not offer an ideal means for diagnosing ovulatory failure. However, when a number of cycles have been followed, in some instances we were able to establish a diagnosis of anovulatory menstruation. The preovulatory type of smear prevails for an unusually long period of time; no regression of the cells is observed as it is typical of the post-ovulatory phase and there is no premenstrual picture; the cells in the smear at the time when bleeding occurs show marked cornification. But certainly there might be a variance of opinion as to the applicability of the vaginal smear method for establishing the diagnosis of anovulatory bleeding in some cases. Shorr<sup>8</sup> considers it likely that the lack of uniformity in the appearance of the vaginal smear during the second half of the cycle results from the interaction of both ovarian hormones. "Any variation in the tempo or the extent of their production could be expected to vary the cytology of the vaginal secretion."

After reviewing the literature, Mack<sup>5</sup> concludes that "no confirmatory evidence of the value of vaginal smears for the detection of ovulation has as yet been produced."

From the foregoing discussion, it can be readily inferred that the study of vaginal smears as a diagnostic method has both advantages and disadvantages. Some of these are obvious while others become evident only after experience.

Among the advantages the following present themselves:

*Ease of Collection.*—There is no trauma or discomfort to the patient. There is no bleeding, and there are no aftereffects. The method is readily suited to the study of endocrine disorders in unmarried girls. The patient may collect the specimens herself and bring them to the doctor or laboratory at her convenience. The method permits of daily observations.

*Absence of Risk.*—There is no possibility of infection by introducing bacteria into the uterus, nor by lighting up latent adnexal disease. During a sterility investigation, a very early pregnancy might not be recognized by clinical observation. Obtaining smear specimens, the study of which might be revealing, will not lead to abortion.

*Diagnostic Potentialities.*—The method affords valuable information in cases of ovarian failure, particularly when there is severe estrogen deficiency. It is possible to check the response of the patient to estrogenic therapy at frequent intervals. Ofttimes the effect of treatment can be objectively proved in the smear—though vaginal cytology is not an absolutely reliable index for therapeutic response. Another advantage is that microscopic bleeding can be readily detected.

Among the disadvantages the following may be listed:

*Difficulty of Interpretation.*—Except in severe estrogenic deficiency cases, it is not possible to arrive at a definite conclusion based on this method alone unless one has given considerable time to the study of vaginal cytology. Even then, the method is not entirely dependable particularly so if it involves making a differential diagnosis of an ovulatory or an anovulatory cycle or determining the time of ovulation. There is an almost infinite gradation of types of cells and both the individual cell and the entire picture must be considered. Furthermore, the presence of infection modifies the smear. These changes are most striking in conditions such as cervicitis or vaginitis. No two cycles are exactly the same. The time of ovulation in some instances may be characterized by a leucocytic exodus; in others, this does not take place. In short, specialized training is a necessity, and the method is suited to the trained pathologist or to the physician especially interested in gynecologic endocrinology rather than to the general practitioner.

*Time Element.*—In most cases it is essential to study a series of slides throughout a menstrual cycle. To obtain the desired information, repeated observations are necessary, particularly if the presence or absence of ovulation is questionable.

### Endometrial Biopsy

According to Herrell,<sup>9</sup> Westphalen,<sup>10</sup> who published his work in 1896, was probably the first to study the endometrium in relation to the menstrual cycle. Several years later Hirschmann and Adler<sup>11</sup> gave their classical description of the histologic changes occurring in the uterine mucosa. These investigators divided the human cycle into four stages: the postmenstrual phase, the interval phase, the premenstrual phase, and

the menstrual phase. Novak<sup>12</sup> in a recent work still adheres to the classification of the cyclic changes in the endometrium as proposed by Hitschmann and Adler. In the light of their findings and with the subsequent recognition of the relationship between endometrial changes and the function of the ovarian hormones, histologic investigations of the endometrium in bleeding disorders caused by endocrinopathies were greatly stimulated. For instance, the significance of endometrial hyperplasia in certain cases of metrorrhagia was clearly demonstrated. Also, much was learned about anovulatory cycles by means of endometrial biopsy.

The instrument we have been using to obtain endometrial biopsy specimens is a cannula curette as devised by Randall.<sup>13</sup> The tissue specimens are fixed in Buoin's solution embedded in paraffin, cut and mounted, and the sections stained for microscopic examination.

The following short, concise summary of the normal cyclic alterations in the endometrium bears repetition—it is based on the description of these changes as given by Campbell, et al.<sup>14</sup>

1. *Follicular Phase*.—The characteristic feature is cellular proliferation indicated by the presence of numerous mitotic figures in the stroma and especially in the glandular epithelium. The endometrium increases in thickness and vascularity and both stromal and glandular cells increase in size. The nuclei of the glands remain in contact with the bases of the cells. No glycogen or mucin is present. The lumina of the glands are round and regular, and there is a thin, albuminous secretion present. Early in the follicular phase the stroma is somewhat loose, but later on becomes progressively more dense. Toward the end of the follicular phase proliferation becomes much slower, mitotic figures are fewer and the glands present a somewhat wavy form upon longitudinal section.

2. *Luteal Phase*.—Here the first characteristic manifestation is the elevation of the nuclei from the bases of the cells of the glandular epithelium producing a conspicuous basal clear zone. This clear zone is filled with masses of glycogen which push the nuclei up toward the lumina. There is a rapid reduction in the number of mitotic figures and there are enlargement and pronounced elongation of the cells lining the endometrial glands. The entire endometrium becomes thicker during this period. However, this thickening does not keep pace with the increase in the size of the glands which results from enlargement of the secreting cells and dilatation of the glands with secretion. As a consequence, the glands become coiled and tortuous. The enlargement and crowding of the secretory cells produce the tuftlike protrusions into the gland lumen. The lumen on longitudinal section exhibits the typical sawtooth appearance. Coiling of the glands is most noticeable in the middle layers of the endometrium, their tortuosity becoming so great that the stroma cells are crowded out and are forced up toward the surface of the endometrium. This proliferation divides the endometrium into three distinct zones. The superficial zone (*Zona compacta*) is composed of relatively straight glands separated by masses of stroma cells. The middle zone (*Zona spongiosa*) is composed of many coiled glands with hardly any interstitial cells between them. The deepest layer of the endometrium (*Zona basalis*) is only slightly affected by the cyclic changes.

Late in the luteal phase the columnar cells which line the endometrial glands have now discharged most of their glycogen and appear shrunken and the lumina become even more ragged in outline. The endometrial arterioles assume a definitely spiral shape. Stroma cells of the compacta which have been gradually increasing in size now become definitely edematous, their fibrillar character has been entirely lost and their polygonal cell walls are now definitely seen. These cells have the characteristic decidual appearance, but this is not a true decidua. The presence of glycogen in the stromal cells which is a characteristic feature of true decidua is not observed. Finally, congestion and leucocytic infiltration herald the next menstruation period.

It becomes immediately evident from the above that the histologic characteristics of the endometrium during the second half of the normal cycle are as readily recognizable as those seen during the proliferative phase. However, the histologic appearance of biopsy specimens from patients with ovarian dysfunction is more varied. Among the abnormal endometrial patterns encountered by the clinician, and classified so carefully by Kotz and Parker,<sup>15</sup> most clearly defined are the atrophic and hyperplastic endometrium. In evaluating an endometrial specimen, it is very important to consider at which time of the cycle the biopsy was performed. For instance a normal structure occurring at the wrong time of the cycle is indicative of some pathology. It is generally agreed that a secretory endometrium reflects an essentially normal ovarian function, including the occurrence of ovulation; that atrophy of the endometrium, occurring in the menopause and in long-standing amenorrhea, is associated with severe ovarian failure; that a hyperplastic endometrium, usually accompanied by functional uterine bleeding, is an indication of an abnormally marked estrogen effect; and finally that a persistently follicular pattern of the endometrium just before the expected date of menstruation indicates absence of ovulation.

As with the vaginal smear, the study of endometrial biopsy specimens, as a diagnostic method, has both advantages and disadvantages. Among the advantages the following present themselves:

1. *Simplicity of Procedure.*—The actual operation of obtaining the biopsy specimens occupies only a short time. The technique when carried out under strictest aseptic precautions by a well-trained individual is safe, requiring only simple instruments, and very rarely anesthesia or hospitalization. It is feasible to study successive specimens which, as Hamblen<sup>16</sup> states, "permits an inference being drawn as to the approximate levels of ovarian function, as manifested spontaneously or as altered by therapy."

2. *Diagnostic Potentialities.*—The endometrium reflects the presence or absence of progesterone production and thus gives correct information regarding ovulation, the occurrence of which can be determined in most cases with a single specimen. Persistent anovulatory cycles may be easily diagnosed with several premenstrual biopsies during successive cycles.

Among the disadvantages may be listed:

1. *Risks Involved.*—Lighting up of a latent adnexal disease is possible, and the method is contraindicated in the presence of pelvic pathology. In any case, there is some discomfort to the patient and slight bleeding during and shortly after the procedure. Pregnancy, unless ruled out previously, may sometimes be interrupted when an endometrial biopsy is performed. In very early pregnancy this interruption may be inevitable.

2. *Shortcomings of Interpretation.*—The technique does not allow investigation of the entire endometrium. Thus the specimen obtained might not truly reflect the ovarian function because of the different histologic patterns sometimes present in various areas of the uterine cavity. Consequently, it is advisable that more than a single biopsy specimen be used for diagnostic purposes. Another shortcoming is that the exact time of ovulation cannot be determined.

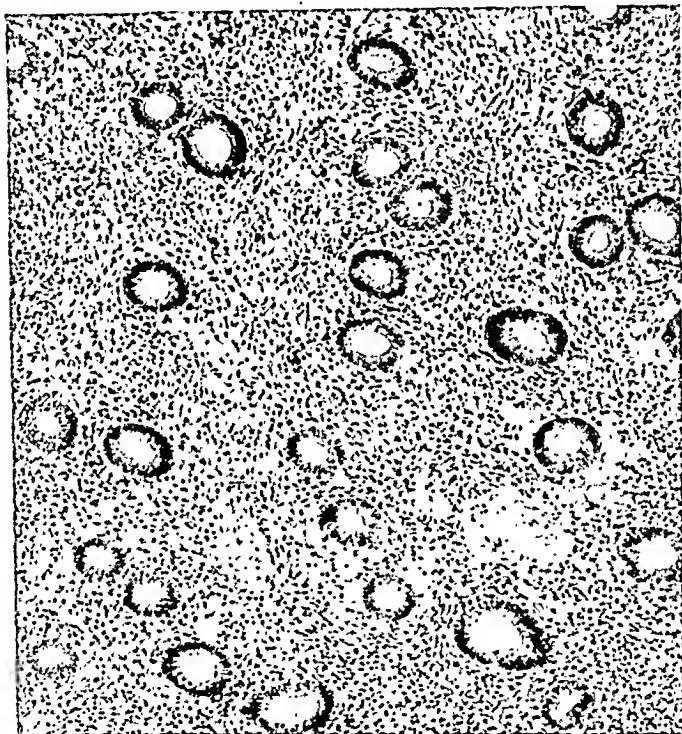


Fig. 1.—Midfollicular phase of endometrium, absence of any luteal change.

3. *Other Disadvantages.*—In virgins endometrial biopsies may be unobtainable. Finally, small areas of malignancy may be missed.

Of the many observations made in the course of this study, we are presenting only a few which will clearly exemplify the foregoing.

Patient C. consulted us because her marriage of several years' duration had remained barren. She stated she had menstruated regularly ever since her menarche at the age of 14. General physical and gynecologic examination, including the Rubin test, revealed no evidence of a pathologic condition. A semen analysis of the husband was satisfactory in every respect. It was attempted to corroborate a tentative diagnosis of anovulatory bleeding by both an endometrial biopsy and a vaginal smear. The endometrial biopsy (Fig. 1) taken two weeks after cessation of menstruation shows no attempt at a luteal phase. On the other hand,



the vaginal smear (Fig. 2) exhibiting many anuclear cornified cells may be interpreted as premenstrual. Occasional cornified cells, many leucocytes, and occasional red blood cells, might be interpreted as post-menstrual. It is very difficult to differentiate in this instance. Thus, the endometrial biopsy permits a clear-cut diagnosis of an anovulatory cycle while the single vaginal smear specimen does not throw light upon the problem.

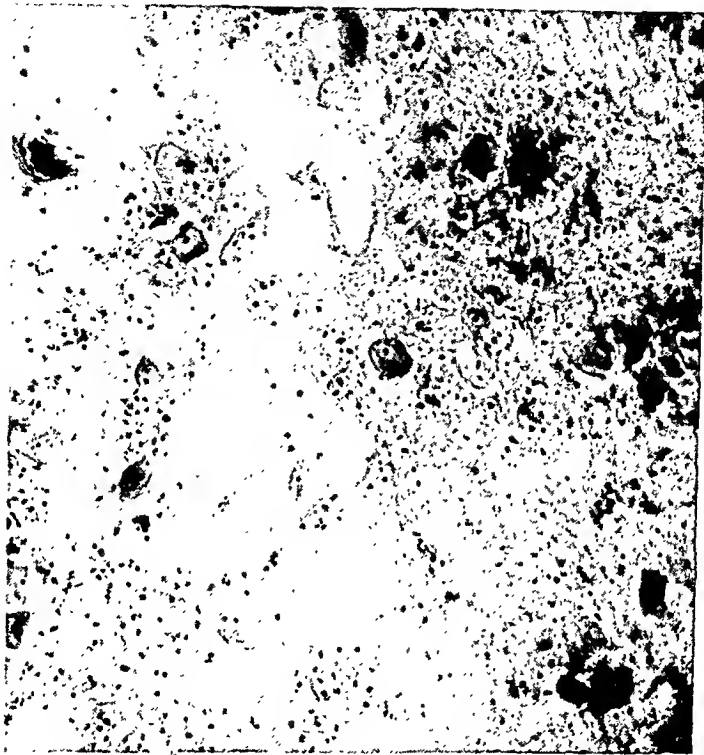


Fig. 2.—Vaginal smear shows occasional cornified cells, anuclear cornified cells, many leucocytes, occasional red blood cells, and superficial cells. This smear does not illustrate any particular phase of a normal cycle.

Whether vaginal smear specimens or endometrial biopsies more clearly reflect corpus luteum hormone activity could be quite definitely shown in surgically castrated women, in whom any effects upon vaginal secretion and endometrium respectively are a mathematical function of any hormonal compounds previously administered. One of us<sup>17</sup> had shown that in human castrates the ingestion of estradiol and pregnenolone properly timed produced secretory changes of the endometrium. It was these experiments which we repeated for proper assessment of the present problem. Illustrative of these trials are the following cases:

Patient M. S., aged 33 years, had had no menses for 9 years following a bilateral salpingo-oophorectomy. Gynecologic examination revealed atrophic external genitalia with a small vaginal orifice. The cervix was atrophied and the retroflex uterus measured 2 inches from external os to fundus. Four mg. estradiol\* daily were given for 12 days.

\*The estradiol (Dimenformon) and pregnenolone (Progestoral) administered to these and all our other patients were kindly supplied by Dr. Pirk of the Roche-Organon Company.



Fig. 3.—Human castrate. Late luteal phase of endometrium following dimenformon and pregnenolone medication.

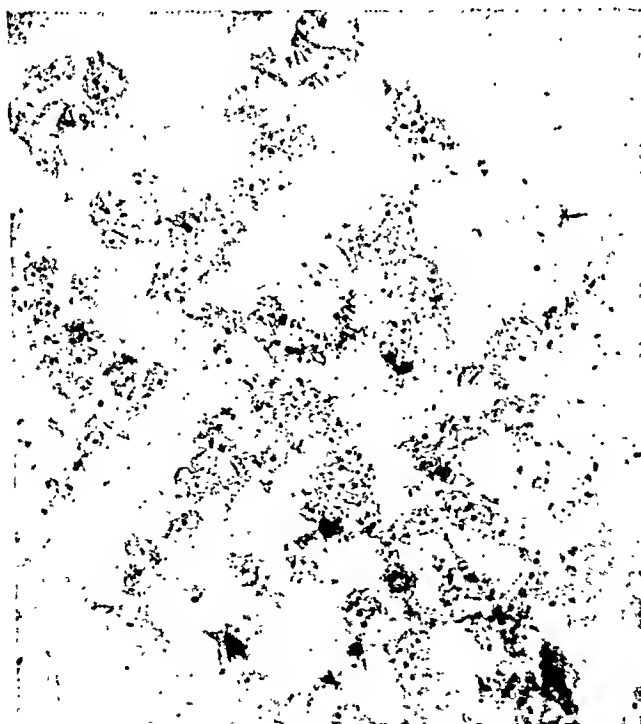


Fig. 4.—Vaginal smear shows insufficient action of estrogen, no cornification and is not indicative of any progestogenic influence.

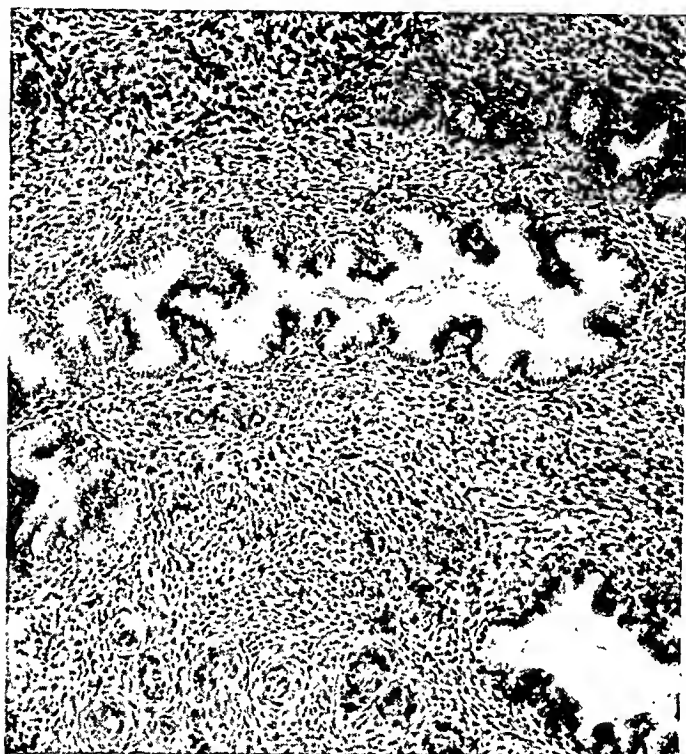


Fig. 5.—Human castrate. Good luteal phase of endometrium following dimenformon and pregnenolone medication.



Fig. 6.—Vaginal smear shows groups of cornified cells and some superficial cells. This is considered good estrogenic action but no progestogenic influence.

This medication was followed by a dose of 6 mg. estradiol plus 100 mg. pregnenolone\* daily for 12 days. Thus within 24 days a total of 120 mg. estradiol and 1,200 mg. pregnenolone was administered. While the premedication biopsy had revealed an atrophic endometrium, the post-medication biopsy (Fig. 3) shows a luteal phase clearly reflecting the previous hormone administration. Yet, the vaginal smear (Fig. 4) taken at the same time as the postmedication biopsy, shows insufficient action of estrogen, no cornification, and is not indicative of any progestogenic influence. This smear certainly is of no diagnostic value.

In another human castrate, R. M., with the usual menopausal symptoms, biopsy shows an atrophic endometrium and the vaginal smear corresponds to her estrogen deficiency state. There were many deep cells with pus, indicating menopause. Following administration of 120 mg. estradiol and 1,200 mg. pregnenolone, given as before outlined, biopsy reveals a fairly good luteal phase (Fig. 5) reflecting the use of progestogenic hormone. However, the vaginal smear specimen (Fig. 6) taken at the same time as the postmedication biopsy shows groups of cornified cells and some superficial cells. This is considered a fair amount of cornification but there is no indication of any corpus luteum action.

### Summary

In summary then, for practical purposes the vaginal smear method, in most instances, will yield correct information regarding estrogen elaboration during the proliferative phase of the cycle. The technique is simpler than that of endometrial biopsy but particularly during the progestational phase it is oftentimes very difficult to evaluate the smear picture, to say the least. If information regarding progestogenic activity or ovulation is sought, the endometrium will serve as a reliable indicator. The vaginal smear, on the other hand, does not give any definite indication of corpus luteum action and thus no clue as to whether or not ovulation has taken place.

I wish to express my grateful appreciation to Dr. Walter T. Dannreuther for his kind assistance and efforts in making this work possible.

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\*See footnote on page 88.

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Beruti, Josue A.: The Problem of Natal Mortality, Arch. Clin. obst. y ginec. "Eliseo Canton" 1: 29, 1942.

Josue A. Beruti (Buenos Aires) in an introduction to a subsequent statistical study, discusses natal and neonatal mortality as factors involved in the declining birth rate in Argentina. Although infant mortality in general has decreased markedly, there has been an alarming increase in neonatal mortality. Twenty-five per cent of all infant deaths occur during the first three days of life. The author considers that stillbirths should also be included in a study of infant mortality and that gynecologists and obstetricians should be concerned with the possibility of reducing their incidence by more intensive application of the principles of hygiene, preventive medicine, obstetrics and pediatrics. Because of varying definitions of natal mortality, official statistics on the subject are hopelessly confused. In Buenos Aires a lapse of three days is allowed between birth and registration, thus death of a child within this time is recorded as a stillbirth. The author defines the categories which he uses in his statistical study. A viable child born without heartbeats is considered a stillbirth; a child of less than 2,500 Gm. is called premature; "newborn" includes birth to one month.

According to statistics published in the bulletin of the Panamerican Health Office, Feb. 1, 1940, there are few American (N. and S.) countries and cities which have shown a regular and continued decrease in natal mortality, many of which have shown an increase and most showing no definite increase or decrease. Statistics for Buenos Aires (Municipal Statistical Review) during the period 1914 to 1939 shows in general a descending tendency (maximum 1923, 5.3 per cent, and minimum 1939, 2.6 per cent). The decrease is almost constant since 1927 and absolutely constant since 1934. According to De Rudder, the neonatal mortality of the world has increased slightly.

Different laws and customs governing registration of births, differing criteria for determining stillbirths and laxity in reporting births contribute to inaccuracy even in official statistics. In hospitals, especially children's hospitals and maternity centers, the more careful records and better discrimination as to the causes of fetal or infantile deaths make statistics from such sources more valuable, but with its accumulation of complicated cases a hospital does not adequately represent a province or locality. For this reason the statistics which the author is to present, although based on a great number of cases, represent a particular situation. A more complete picture could only be obtained by combining statistics from all maternity centers of all cities and towns in the Republic. Since this is at present Utopian, he confines himself to an investigation of the clinical material from one maternity center in Buenos Aires, hoping that this combined with material from other institutions may yield some instructive facts. The author warns that the statistics are not absolutely perfect since the clinical records, especially in early years, are not all satisfactory and since diagnostic, prophylactic and therapeutic criteria have not remained constant through the years.

J. P. GREENHILL.

# DEMEROL (S-140) AND SCOPOLAMINE IN LABOR

## A Study of 1,000 Cases

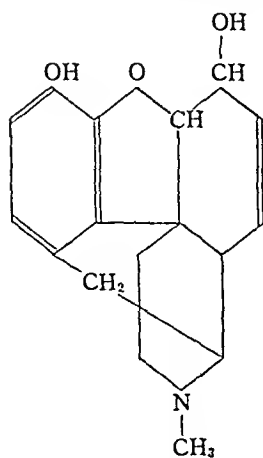
WILLIAM R. SCHUMANN, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School and the Boston Lying-in Hospital)

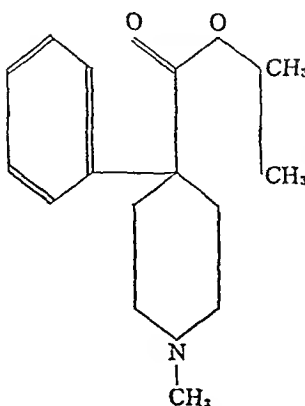
SINCE the practice of administering analgesic drugs in labor was begun at the Boston Lying-in Hospital in 1931, a constant effort has been made to find a medication routine which would afford complete amnesia for the mother, yet would produce no untoward effects in either mother or baby. Because we believe scopolamine to be the amnesic drug of choice, it has been incorporated in our medication routine. The adjuvant, be it morphine, barbiturate, paraldehyde, or Demerol, is used for its contributory soporific or analgesic effect. The psychic sedation obtained thus provides a favorable background for the action of scopolamine, reducing the excitement and enhancing the amnesia. Because the drugs commonly employed at present for this purpose are not ideal, Roby and Schumann<sup>1</sup> initiated the clinical study of Demerol<sup>2</sup> in conjunction with scopolamine as an obstetric analgesic at this clinic. It is the purpose of this paper to report the completion of our studies on one thousand cases.

### Material

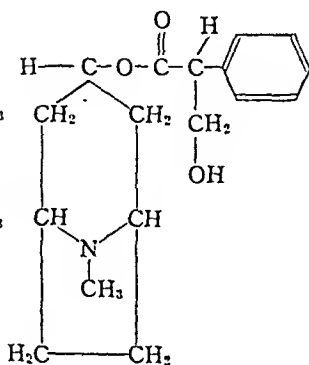
Demerol (1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester) was first described in 1939 by Eisleb and Schaumann<sup>2</sup> under the proprietary name Dolantin. It is a synthetic which exhibits properties analogous to both the atropine and morphine series (Schaumann,<sup>3</sup> Duguid and Heathcote,<sup>4</sup> Gruber, et al.,<sup>5</sup> Barlow and Hamburger,<sup>6</sup> Batterman<sup>7</sup>), although much weaker than atropine as a spasmolytic agent, and displaying properties midway between codeine and morphine as an analgesic. It differs from morphine in that it relaxes smooth muscle rather than causes spasm.



MORPHINE



DEMEROL



ATROPINE

\*The Demerol used in this study was generously supplied by the Winthrop Chemical Company, New York, N. Y.

The appealing property from an obstetric standpoint is the apparent absence of any significant narcotic depressant action, both in experimental (Schaumann,<sup>3</sup> Barlow and Hamburger,<sup>6</sup> Gruber, et al.,<sup>5</sup> Duguid and Heathcote<sup>4</sup>) and clinical (Batterman<sup>7</sup>, Gilbert and Dixon,<sup>8</sup> Rovenstine and Batterman,<sup>9</sup> Roby and Schumann<sup>1</sup>) studies.

Demerol has no demonstrable effect on either the urine or blood picture (Hecht<sup>10</sup>). Batterman<sup>7</sup> reports a loss of gut motility in 84 per cent of patients studied, abolition of corneal reflex in 80 per cent, and no cases of primary addiction. Studies made by Himmelsbach<sup>11</sup> suggest that the risk of addiction would be negligible in doses employed obstetrically.

Side effects have been reported by several observers (Hecht,<sup>10</sup> Meyer,<sup>12</sup> Barlow, et al.,<sup>6</sup> Gilbert and Dixon,<sup>8</sup> Davis<sup>13</sup>), Batterman<sup>7</sup> finding the incidence to be 25.5 per cent in his hospitalized patients. He notes such effects in order of frequency as dizziness, nausea, pallor, diaphoresis, and dryness of the mouth. Respiratory depression was noted in only two markedly debilitated patients out of 774 cases. There is agreement that intravenous administration is attended by a higher incidence of side effects (Davis,<sup>13</sup> Meyer<sup>12</sup>), and Meyer<sup>12</sup> has tentatively concluded that intravenous administration may be hazardous. Following a 100 mg. dose to control hiccup, he observed profuse perspiration, nausea, emesis, temporary loss of consciousness, a rapid, thready pulse, and irregular respiration.

### Method

Discrepancies in dosage and frequency of medication are inevitable when analgesia is ordered as needed by the house-officer on duty. To avoid such inequalities, a routine of medication was adopted for purpose of this study. All patients admitted to the hospital in labor were thereby insured identical medication, given at stated intervals. Although more practical on a busy service with two daily shifts of house-officers, this method has the disadvantage of inflexibility; no adjustment in dosage can be made for variations in body weight and rate of metabolism. Standing medication orders were as follows:

#### Routine medication:

(Unless otherwise stated, all medication is given intramuscularly.)

##### Initial medication:

Demerol 100 mg.	}	Given when patient begins to mind her pains. Given 45 minutes later.
Scopolamine gr. $\frac{1}{100}$		
Scopolamine gr. $\frac{1}{150}$		

##### Second medication:

Demerol 100 mg.	}	Given 4 hours after first medication.
Scopolamine gr. $\frac{1}{200}$		

##### Subsequent medication:

Demerol 100 gm.	Given every 4 hours.
Scopolamine gr. $\frac{1}{200}$	Given every 3 hours.

#### New admissions expected to deliver within 2 hours:

##### Initial medication:

Demerol 50 mg.	}	Slow intravenous administration on admission. Intramuscular administration on admission.
Scopolamine gr. $\frac{1}{200}$		
Demerol 50 mg.		
Scopolamine gr. $\frac{1}{200}$		

Subsequent medication to be given as per routine above.

#### Premedication for cesarean sections:

Demerol 50 mg.	}	Intravenously	}	Given 45 minutes prior to anesthetic induction.
Scopolamine gr. $\frac{1}{200}$				
Demerol 50 mg.				
Scopolamine gr. $\frac{1}{200}$				

The following alterations in routine were instituted during the course of the study as we became more familiar with the action of the drug:

**Routine medication:**

Subsequent scopolamine medication (gr.  $\frac{1}{200}$ ) was given at 2- instead of 3-hour intervals.

New admissions expected to deliver within 2 hours:

Demerol 100 mg.	}	Slow intravenous administration on admission. Minimal 2 minutes for 2 c.c. 100 mg.
Scopolamine gr. $\frac{1}{100}$		

Premedication for cesarean sections:

Demerol 100 mg.	}	Slow intravenous administration 45 minutes prior to induction.
Scopolamine gr. $\frac{1}{100}$		

**Standing Nursing Orders:**

1. Prior to initial medication, patient is urged to void, and canvas bed-sides are placed on bed. Dentures are removed.
2. On administering initial medication, patient is told that she is receiving the medicine which will put her to sleep and prevent her feeling more pain.
3. No further conversation is held with patient.
4. Any deviation from routine of medication must be checked by resident physician before medication is given to patient.

**Evaluation**

*Amnesia.*—Each patient was interviewed the day following her delivery. She was requested to relate everything she could remember after receiving the initial medication, and leading questions were avoided.

The first 112 cases were interviewed by one examiner (Roby). Of the remaining 898 cases, 676 were interviewed by one examiner (W. R. S.), while 222 were seen by a third examiner (M. A.). This restriction on the number of examiners was made in an effort to minimize subjective variations in appraisal. The following arbitrary classification of amnesia was adopted:

1. Absolute amnesia.
2. Patient able to recall isolated incidents (being moved from labor room to delivery room, being moved from bed to delivery table, and having anesthetic mask applied), but recalling neither orderly sequence nor pain.
3. Patient able to recall a number of incidents in orderly sequence, but remembering little or no pain. In effect, poor amnesia but satisfactory analgesia.
4. Failure of amnesia or analgesia.

*Effect on Newborn Infant.*—To evaluate the immediate depressant effect on the newborn infant, the following arbitrary classification was adopted:

- A. Infant breathes spontaneously with no resuscitation other than routine inversion and aspiration of upper airway with rubber ear syringe.
- B. Infant requires administration of oxygen and/or warm blanket, but resumes spontaneously within 2 minutes.
- C. Infant requires more than 2 minutes of resuscitation before breathing spontaneously. Also any infant whose condition following delivery merits observation by the pediatrician.



Evaluation of persistent damage to the newborn infant is tabulated from the pediatrician's discharge examination on all "C" babies.

### Maternal Effects

*Amnesia.*—The initial 112 cases have been previously reported (Roby and Schumann<sup>1</sup>) as "Good" and "Poor" amnesia as shown in Table I. Because "Good" embraces groups 1 and 2, while "Poor" includes groups 3 and 4, these original cases will not be included in the analysis.

TABLE I. SHOWING AMNESIA IN ORIGINAL 112 CASES (ROBY AND SCHUMANN<sup>1</sup>)

AMNESIA	NUMBER OF CASES	PERCENTAGE
Good	97	84.8
Poor	15	15.2

Seventeen cesarean sections will be considered under separate head, and 34 cases have been discarded because they were prematurely medicated and subsequently permitted to come out of their analgesia. There remain 847 cases (Table II), in which it is seen that groups 1 and 2 (entirely satisfactory), comprise 70.5 per cent of the series.

TABLE II. SHOWING AMNESIA IN SUBSEQUENT 847 CASES

AMNESIA	NUMBER OF CASES	PERCENTAGE
1. (Absolute amnesia)	286	33.8
2. (Isolated incidents)	311	36.7
3. (Analgesia but no amnesia)	143	16.9
4. (Failure of amnesia)	107	12.6

In examining groups 3 (analgesia but no amnesia) and 4 (failure of amnesia), it became apparent that a number of cases had received medication too late to benefit materially from its effects, while a few had not been medicated as frequently as called for in the routine. If the fault in these cases be thought to lie in the administration rather than in the drug itself, then the corrected failure groups of 43 in group 3 and 38 in group 4 are seen to comprise 5.1 per cent and 4.5 per cent respectively of the entire group, or a total of 9.6 per cent.

TABLE III. SHOWING RELATION OF DURATION OF MEDICATION TO AMNESIA

GROUP 3 (GOOD ANALGESIA WITHOUT AMNESIA)	
Initial dose within 1 hr. of delivery	48
Initial dose within 2 hr. of delivery	37
Excessive interval between doses	6
Unqualified failure of amnesia	43
GROUP 4 (COMPLETE FAILURE)	
Initial dose within 1 hr. of delivery	55
Initial dose within 2 hr. of delivery	24
Excessive interval between doses	2
Unqualified failure	38

These figures are found to compare favorably with the extensive barbiturate-scopolamine series studied previously in this hospital (Irving et al.<sup>13</sup>), in which pentobarbital-scopolamine yielded an 86 per cent satisfactory amnesia.

### Effect on Length of Labor

It is our impression that data on duration of labor need be regarded with reservation, for it is indeed difficult to appraise accurately the time of onset of labor. The following data are presented for comparison with other series. Curiously enough, the figures closely approximate those of Gilbert and Dixon,<sup>8</sup> who used demerol in conjunction with barbiturates, and who noted an average primiparous labor of 11.8 hours,

TABLE IV. SHOWING AVERAGE LENGTH OF LABOR

	PRIMIPARA	MULTIPARA
Total labor	12.4 hr.	7.6 hr.
First stage	10.6 hr.	6.8 hr.
Second stage	1.8 hr.	.8 hr.

an average multiparous labor of 7.1 hours. Rathbun,<sup>15</sup> in reviewing a series of 500 cases delivered under barbiturate-scopolamine analgesia at this hospital, found the average primiparous labor to be 14.9 hours, the average multiparous labor to be 8.8 hours. Thus, under the demerol routine, the average primiparous labor has seemingly been reduced by 2.5 hours, and the multiparous labor by 1.2 hours. This represents a 17 per cent and 14 per cent reduction, respectively, which would appear to be significant.

### Preanesthetic Effect

No statistics have been collected on anesthetic complications of induction in this series, but it is the opinion of the Director of Anesthesia (Hershenson<sup>16</sup>) that demerol-scopolamine as given in this routine is not surpassed by other preanesthetic combinations in common use at present. There have been no major pulmonary anesthetic complications in the series, and we have enjoyed complete freedom from the pulmonary edema crises seen occasionally with barbiturates.

In order to gain an approximate estimate of what effect, if any, demerol might exert on the quantity of anesthetic agent required, the amount of anesthetic agent used was carefully measured on 18 uncomplicated pelvic deliveries in the demerol series. For comparison, the same observations were made on 19 uncomplicated pelvic deliveries where the patients had received seconal gr. 3, sodium amytal gr. 6, and scopolamine gr. 1/100. All anesthetics were administered by the Di-

TABLE V. SHOWING AMOUNT OF ANESTHETIC AGENT REQUIRED

CARBON DIOXIDE ABSORPTION METHOD			
ANALGESIA	NUMBER OF CASES	AVERAGE AMT. VINETHENE	AVERAGE AMT. ETHER
Demerol-scopolamine	10	25 c.c.	20 c.c.
Seconal-Na amytal-scopolamine	13	26 c.c.	23 c.c.
OPEN DROP METHOD			
ANALGESIA	NUMBER OF CASES	AVERAGE AMT. VINETHENE	AVERAGE AMT. ETHER
Demerol-scopolamine	8	18 c.c.	91 c.c.
Seconal-Na amytal-scopolamine	6	19 c.c.	75 c.c.

rector of Anesthesia. The above data (Table V) show little significant variation in the amount of anesthetic agent required in each group, and suggest that demerol and the barbiturates are equivalent in preanesthetic value.

### Intravenous Use

The multipara admitted in active labor has heretofore presented a problem in obstetric analgesia. She frequently vomits oral medication and expels rectal medication, and even though she retains it, is usually delivered before the therapy becomes effective. Such difficulties led us to investigate the intravenous use of demerol-scopolamine analgesia. With our first 107 cases, we employed only half the initial dose intravenously, giving the remainder intramuscularly. When it became apparent that intravenous administration was not hazardous, we gave the entire initial dose intravenously with improved amnesic results, as may be seen in Table VI. That these results were obtained in patients who would have shown little response to oral or rectal medication is emphasized by Table VII. Here it is noted that 64 per cent of the 50 mg. group and 62 per cent of the 100 mg. group were medicated for less than one hour.

TABLE VI. SHOWING AMNESIC EFFECT WITH INTRAVENOUS MEDICATION

DOSE EMPLOYED	AMNESIA CLASSIFICATION								(NO. OF CASES) TOTAL
	1	%	2	%	3	%	4	%	
50 mg. IM-50 mg. IV	28	26	39	36	28	26	12	12	107
100 mg. IV	6	21	16	55	5	18	2	6	29

TABLE VII. SHOWING LENGTH OF TIME ELAPSED FROM MEDICATION TO DELIVERY

DOSE EMPLOYED	NO. OF CASES					TOTAL
	1 TO 15 MINUTES	16 TO 30 MINUTES	31 TO 45 MINUTES	46 TO 60 MINUTES	OVER 1 HOUR	
50 mg. IV-50 mg. IM	8	17	4	29	49	107
100 mg. IV	5	9	2	2	11	29

### Untoward Effects

The only unpleasant side effects noted in this series were in the patients receiving intravenous medication. With the exception of vomiting, no further untoward results were seen after we learned to give the drug slowly, taking at least two minutes by the clock to administer 2 c.c. (100 mg.). If the demerol-scopolamine mixture is given rapidly, the patient invariably vomits immediately, and over a transient 30 to 40 seconds, the pulse becomes rapid, irregular, and thready, with a gradual return to normal. The patient will ordinarily vomit two to three times before becoming drowsy, listless, and quiet.

If the drug is given slowly, about one-fourth of the patients will experience transient nausea, and may or may not vomit. If vomiting occurs, it is usually only once. The customary course is a pleasant sensation of warmth and euphoria, and a number of patients have felt as though they were floating up from the mattress. The patient next experiences a feeling of numbness, as though the whole body had "gone to sleep," and becomes quiet. She may respond lucidly to questions, but shows an increasing disinclination to respond, until finally she becomes disoriented in her response. From this point on, if adequate dosage is maintained, the patient will ordinarily sleep quietly between her pains. During a pain, she may rouse, attempt to move about or sit up in bed, mumble or cry out, and then relapse into quiet sleep when the pain has passed.

We have been unable to keep an accurate record of the incidence of excitement. It is our impression that a manic state occurs with about the same frequency as in barbiturate-scopolamine analgesia, and we believe that such excitement is the result of scopolamine idiosyncrasy, rather than an effect of the adjuvant, be it barbiturate or demerol. In general, however, the labor room has been noticeably quieter since the demerol routine supplanted both barbiturate and paraldehyde analgesia.

For the obstetrician accustomed to the use of barbiturates, we should like to include the observation that the demerol-scopolamine patient, even though adequately medicated, may respond to questions with a disconcerting lucidity. If, however, a medication routine similar to that used in this series has been adhered to, the amnesic result will be found comparable to that obtained with barbiturates.

### Analgesic Effect

During a process such as labor, it would seem to be pharmacologically sound to use a true analgesic drug in conjunction with scopolamine if we are attempting to suppress the ascent of pain impulse to the level of consciousness. That demerol exerts a gratifying analgesic effect may be seen in Table VIII, which represents a group of 37 patients who

TABLE VIII. SHOWING ANALGESIA IN ABSENCE OF ANESTHESIA

Complete amnesia	9
Isolated incidents	10
No amnesia but no pain	10
Pain during delivery	8
Total	37

precipitated without anesthesia. Of these, 29, or 79 per cent, were delivered with no recollection of pain whatever, in spite of the fact that several patients sustained lacerations requiring repair.

### Effect on the Newborn Infant

In the original 112 cases, Roby and Schumann<sup>1</sup> reported 16 slow babies. To permit a more detailed analysis, we shall present data on the remaining 897 cases, using the criteria previously described.

TABLE IX. SHOWING INCIDENCE OF FETAL MORBIDITY AND MORTALITY

CLASSIFICATION	NUMBER	PERCENTAGE
A (Active)	737	82.15
B (Slightly slow)	107	11.99
C (Slow)	30	3.3
Neonatal deaths	6	0.66
Stillborn	17	1.9

All of the babies in the B (slightly slow) group were normal on leaving the delivery floor and required no further attention. Of the thirty C (slow babies), 28 were discharged with the mother as normal, showing no demonstrable sequelae. Two were discharged for further follow-up with a diagnosis of severe asphyxia and cerebral damage.

It may be noted from the following protocol that with the exception of four babies, there is an adequate obstetrical explanation for the slowness of the newborn infant. Of the four slow babies following an uneventful labor and delivery, all were discharged as normal with the mother.

It will be noted from the foregoing protocols that each of the stillborns and neonatal deaths is readily explainable on the basis of con-

## PROTOCOL I. SHOWING DISPOSITION OF C (SLOW) BABIES

DISCHARGED AS NORMAL	
97253	Mid transverse arrest. Pituitrin stimulation. Easy delivery.
97292	Seventeen-hour first stage. Two-hour second stage.
97299	Uneventful delivery. Observation only 2 days.
97327	Seventeen-hour first stage. Two-hour second stage. Fetal distress.
97427	Five pounds. Discharged from premature nursery on seventh day.
97434	Twin No. 2. Primiparous breech, forceps to aftercoming head.
97508	Persistent posterior. Manual rotation and low forceps.
97520	Uneventful delivery.
97534	Four and three-quarter-hour second stage with subsequent cesarean section for cephalopelvic disproportion.
97581	One-hour second stage with fetal distress.
97661	Secondary uterine inertia. Pituitrin stimulation.
97702	Mid transverse arrest with Barton forceps extraction.
97807	Uneventful delivery.
98068	Cord tightly about neck 1 x. Overnight observation only.
98119	Low forceps for outlet arrest. Overnight observation only.
98127	Secondary uterine inertia with pituitrin stimulation.
98181	Primiparous breech with forceps to aftercoming head.
98208	Manual flexion of multiparous face presentation.
98230	Uneventful delivery.
98311	Fetal distress. Cord about neck 1 x.
98334	Placenta previa.
98592	Manual rotation for persistent posterior. Low forceps.
98744	Uneventful delivery. Forceps abrasion to cheeks only.
99727	Manual rotation for persistent posterior. Low forceps.
99732	Fetal distress. True knot in cord.
99847	Fulminating pre-eclampsia, grade II, on veratrine with induction of labor by rupture of membranes.
100476	Mid transverse arrest with difficult forceps extraction.
DISCHARGED AS ABNORMAL	
97669	Manual rotation and low forceps for outlet contraction. Cephal-hematoma and marked hyperactivity. Diagnosis—severe asphyxia with possible cerebral damage.
97754	Eleven-hour labor with 1½-hour second stage. Persistent midtransverse arrest with manual rotation and midforceps extraction. Discharged from observation on twenty-first day with diagnosis of severe asphyxia and cerebral damage.

## PROTOCOL II. STILLBORN

97182	Anencephalic.
97281	Extensive intracranial hemorrhage. Liver 2 x normal.
97625	Monster with multiple congenital abnormalities.
97644	Erythroblastosis.
97799	Dead on admission.
97828	Macerated 2-pound infant.
97896	Anencephalic.
97995	Erythroblastosis.
98066	Dead on admission. Cord 3 x about neck.
98122	Fetal heart disappeared 38 minutes before delivery. Cord 1 x tightly about neck.
98148	Hydrocephalus and spina bifida.
98265	Erythroblastosis.
99740	Two-pound 5-ounce primiparous breech.
99860	Probable erythroblastosis.
100221	Diabetic mother. Dead on admission.
100399	Four-pound 8-ounce twin No. 1. Pre-eclampsia, grade II.
100532	Dead on admission.

## PROTOCOL III. NEONATAL DEATHS

97467	Died fourth day massive intracranial hemorrhage.
97849	Died third day intracranial hemorrhage. Mid transverse arrest with difficult forceps delivery.
98574	Died 10 minutes multiple congenital anomalies.
100504	Died 12 hours. Tumultuous 4-hour primiparous labor.
100646	Died 2 hours. Erythroblastosis.
100739	Died 48 hours congenital heart.

genital deformity or pathological state, and it would therefore seem that there is no need to implicate the maternal analgesia as an etiological factor.

## Premature Infants

Realizing that any depressant action of obstetrical analgesia on the newborn would be maximal in the premature group, the following analysis of the premature infants in the series is presented.

## PROTOCOL IV. SHOWING CONDITION OF 44 PREMATURES

CONDITION	WEIGHT		REMARKS
	POUNDS	OUNCES	
A	5	8	
A	4	$\frac{1}{4}$	
A	6	$6\frac{1}{4}$	Twin #1
A	5	12	Twin #2
A	5	5	
A	4	9	
A	5	0	
A	5	$5\frac{1}{2}$	
A	5	9	IV 50 mg.—IM 50 mg.
A	1	0	Died 12 hours of prematurity.
A	5	5	
A	4	$15\frac{1}{2}$	IV 50 mg.—IM 50 mg.
A	4	10	Twin #1
A	5	0	Twin #2
A	5	$13\frac{3}{4}$	Twin #1
A	5	$14\frac{1}{4}$	Twin #2
A	6	11	Twin #1
A	7	5	Twin #2
A	4	14	Twin #1
A	5	$\frac{1}{2}$	Twin #2
A	5	12	Twin #2
A	5	$3\frac{1}{4}$	
A	5	4	
A	3	0	Twin #2
A	5	9	IV 50 mg.—IM 50 mg.
A	5	12	Twin #2
A	3	12	
A	2	13	Twin #1
A	2	14	Twin #2
A	6	10	
A	4	2	IV 50 mg.—IM 50 mg.
A	3	5	Twin #1
A	4	13	Twin #2
A	5	0	
A	5	8	
B	5	0	
B	5	14	Low forceps for fetal distress.
B	5	14	Mother severe cardiac.
B	6	1	Twin #1
B	4	3	
C	2	5	Primiparous breech. Died 12 hours.
C	4	8	Primiparous breech. Died 16 hours.
Stillborn	2	2	Premature separation.
Stillborn		Macerated	Dead on admission.

All B infants responded well and required no further treatment other than usual premature care.

TABLE X. SHOWING CLASSIFICATION OF PREMATURE INFANTS

	NO. OF CASES	PERCENTAGE
A (Active)	35	79.6
B (Slightly slow)	5	11.4
C (Slow)	2	4.5
D (Stillborn)	2	4.5
Total	44	100.0

It will be observed that not only were 91.0 per cent of the prematures in satisfactory condition on leaving the delivery room, but also that there is no correlation between the weight of the baby and the degree of respiratory depression. In point of fact is the 1-pound infant who cried vigorously on delivery, only to succumb later to atelectasis. There is little to suggest a respiratory depressant effect in this group.

### Cesarean Section Group

To avoid narcotizing the fetus, it has been the practice in this clinic to premedicate patients undergoing cesarean section with atropine only. Such minimal premedication renders the anesthetic induction trying to both patient and anesthetist in the case of general anesthesia, while operating under local anesthesia is usually made no easier by an alert, frequently apprehensive patient. When, during the course of this study, it became apparent that demerol exerted no demonstrable depressant effect on the baby, the use of the drug was extended to include the premedication of cesarean section patients.

TABLE XI. SHOWING CONDITION OF CESAREAN SECTION BABIES

NO. OF CASES	CONDITION	AVERAGE LENGTH OF MEDICATION
14	A	30 minutes
2	B	1 hour, 45 minutes
1	C	45 minutes

Of the two slightly slow babies noted in Table XI, one was obtained at operation in which one hour of operating time was consumed before the infant was delivered. The slow baby was delivered following antepartum hemorrhage from a complete placenta previa.

Since the inception of demerol premedication, those patients receiving general anesthesia have been relatively free from mucus and excitement during the induction. Patients undergoing operation with local anesthesia have had uniformly satisfactory amnesia.

### Intravenous Use

That the intravenous use of demerol has no more effect on the fetus than the intramuscular route is shown by Table XII.

TABLE XII. SHOWING FETAL EFFECT OF INTRAVENOUS USE

DOSE	A		B		C		STILLBORN	
	NO.	%	NO.	%	NO.	%	NO.	%
50 IV—50 IM	97	89.8	6	5.6	2	2.8	3	1.8
100 mg. IV	26	89.6	3	10.4	—	—	—	—

In addition, it may be seen that the incidence of active babies is almost identical, whether the patient received 50 or 100 mg. intravenously. Both of the slow babies were discharged as normal with the mother. Of the three stillborns, two were erythroblastotic and dead on admission, while the third was a 2-pound macerated infant.

### Delivery Without Anesthesia

In a group of 37 patients who preecipated without anesthesia, any depressant effect of the analgesia would become apparent, there being no masking by an inhalation anesthetic. As will be seen in Table XIII, all of the newborn infants except 2 were active. The one slow baby was a 4-pound premature delivered following ante-partum bleeding from a ruptured marginal sinus in a grade 1 pre-eclampsie. The stillborn was a 2-pound macerated fetus.

TABLE XIII. CONDITION OF NEWBORN DELIVERED WITHOUT ANESTHESIA

CONDITION	NO. OF CASES
A	35
B	—
C	1
Stillborn	1
Total	37

### Summary and Conclusions

Demerol and scopolamine have been used in a series of 1,000 cases for the purpose of studying the maternal and fetal effects of this combination when used as an obstetrical analgesic. Because our primary purpose in medication is establishing complete amnesia, we incorporate scopolamine in our routine as the amnesic drug of choice. Demerol is used to obtain psychic sedation through its analgesic effect, thereby securing a favorable background for the action of scopolamine, reducing the excitement, and enhancing the amnesia.

1. The uncorrected incidence of satisfactory amnesia is 70.5 per cent, where satisfactory amnesia is taken to mean either absolute amnesia, or at the most, the recollection of two or three isolated incidents where no pain is recalled. If this figure is corrected for cases receiving medication either too late, or so infrequently as to nullify the therapeutic effect, the incidence of satisfactory amnesia rises statistically to 90.4 per cent. It is our opinion that while demerol possesses other properties that make it more desirable for purposes of obstetrical analgesia than the barbiturates, it falls slightly short of the barbiturates in providing satisfactory amnesia as measured by our standards.

2. The average primiparous labor in this series was 12.4 hours, the average multiparous labor 7.6 hours. This is a reduction of 2.5 hours in the primiparous labor and 1.2 hours in the multiparous labor when compared with a series of 500 patients in this hospital who received barbiturate analgesia. Since this represents a 17 per cent and 14 per cent reduction respectively, we believe it to be significant.



3. As a preanesthetic medication, demerol is not surpassed by the other preanesthetic combinations in common use. The amount of anesthetic agent required is approximately the same as in those patients receiving barbiturates. There were no major pulmonary complications.

4. Intravenous administration has been employed in those patients admitted in active labor and expected to deliver within 2 hours. It has also been used for premedicating cesarean sections. The incidence of satisfactory amnesia is approximately the same as in those patients receiving intramuscular medication, despite the fact that 63 per cent of the patients were medicated for less than one hour. No increased hazard has been demonstrated in association with the intravenous route.

5. The only maternal untoward effects in the series were seen in the intravenous group. With the exception of transient nausea in one-fourth of the cases, no further side effects were seen when the drug was administered slowly, taking a minimal two minutes by the clock to inject 2 c.c. (100 mg.).

6. The analgesic properties of demerol are demonstrated by a series of 37 patients delivered without anesthesia, of whom 79 per cent could recall no pain whatsoever.

7. Demerol exerts no demonstrable depressant effect on either full-term or premature infants, whether administered by the intramuscular or the intravenous route.

In view of the satisfactory amnesia, the absence of pulmonary complications, and the freedom from depressant effect on the fetus, it is our opinion that demerol in conjunction with scopolamine is superior as an obstetrical analgesic to other analgesics in common use.

We wish to thank Dr. Bert Hershenson for his assistance in obtaining the data on preanesthetic effect, and Dr. Monrad E. Aaberg for his assistance in interviewing patients.

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## CONTINUOUS CAUDAL ANESTHESIA IN 200 OBSTETRIC PATIENTS

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THE publication of an article in 1942 by Edwards and Hingson<sup>1</sup> on the use of continuous caudal anesthesia created a widespread interest in the subject and since that time numerous reports have been published.<sup>2-12</sup> This article is an analysis of our experience with this method.

### Material

Our study is based on a series of 200 consecutive obstetric patients in whom continuous caudal anesthesia was employed routinely in order to determine its practicability.

In 5 instances, the anesthesia was unsatisfactory and inhalation anesthesia was used in the second stage. In 195, or 97.5 per cent of our cases, the method was successful. The period of anesthesia varied from 30 minutes to 24 hours 30 minutes, with an average of 4 hours 20 minutes for primiparas and 2 hours 45 minutes for multiparas. The average duration of the first stage in the primiparous group was 9 hours 4 minutes and the second stage 34 minutes; while for the multiparas it was 8 hours 12 minutes and 32 minutes respectively.

One hundred-three (103) patients were primiparas and 97 multiparas. A vertex presentation was found in 195 instances, of which 30 were persistent occiput posterior or transverse. There were 2 face\* and 3 breech presentations. A spontaneous termination of labor occurred in 62, or 63.9 per cent of the multiparas, but an operative delivery was necessary in all the primiparas. An episiotomy was employed in 156, and minor lacerations of the perineum occurred in only 8 instances.

Two patients had a pre-eclamptic toxemia. In 2 cases of placenta previa the patients were successfully delivered with the use of hydrostatic bags. Four cases of uterine inertia were encountered, but the careful employment of pitocin in small doses resulted in delivery without difficulty. In 4 patients a test of labor was conducted because of cephalopelvic disproportion, and 2 of these were finally subjected to cesarean section. In one case, the operation was carried out by increasing the dosage of the drug in order to obtain a higher level of abdominal skin anesthesia, and in the other, by changing to an inhalation anesthetic.

### Contraindications

Several important contraindications to the use of caudal anesthesia have been emphasized by various authors. The first was directed to difficulties inherent with the introduction of the needle because of abnormalities of the sacrum, such as variations in the curvature of the sacrum, spina bifida, or failure of fusion of one or more of the poste-

\*An increasing number of face presentations has occurred while using caudal anesthesia with the patients in the modified Sims' position.

rior arches. In a survey of 100 x-ray photographs, we noted that variations in the classical descriptions of the pelvis occurred in four out of five sacra, but probably not one in 100 is extensive enough to preclude the use of continuous caudal anesthesia.

The presence of infective processes about the sacral area is of prime importance. For example, one patient was not given this type of anesthetic because of a generalized folliculitis. The possibility of introducing an infection into the sacral canal must be remembered always as a possible serious complication.

A hypersensitivity to local anesthetic agents also must be kept in mind, but in this series a history of previous manifestations of this type was not obtained.

In some instances, mental or psychic aberrations make it impossible to trust the patient to follow the necessary simple instructions. This was observed in one case and it became necessary to remove the needle after the caudal anesthesia had been started.

### Technique

A distinct advantage in this study was the fact that caudal anesthesia had been employed on our service during the second and third stages of labor in over 500 deliveries previous to the adoption of the continuous method, and we feel that a thorough fundamental training of the operator is necessary for its success.

*Stage of Labor When Anesthetic Is Begun.*—In general, the statement of Edwards and Hingson, that "continuous caudal anesthesia is started when the patient is in labor and in distress," has been our basis for determining when to start the procedure. As a rule, this was found to be when the cervix was dilated 3 cm. and the contractions occurred every five minutes or less and lasted for 20 seconds or more.

*Premedication.*—It is accepted that premedication with barbiturates decreases the toxicity of local anesthetics from 3 to 5 times. For this reason nembutal, seconal, or a combination of sodium amytal and seconal in 3-grain doses was given 15 minutes prior to beginning the anesthesia. Seven patients failed to receive premedication, and one had a moderately severe toxic reaction with hallucinations and clonic muscular contractions. This condition lasted for 90 seconds but did not necessitate abandonment of the anesthetic.

*Drug and Dosage.*—Metycaine was used in all instances. It was prepared by dissolving the powder in normal saline as a 1.4 per cent solution. The initial dose varied from 30 to 45 c.c., with subsequent injections of 20 c.c. at intervals of from 30 to 90 minutes, with an average of 50 minutes. The total amounts employed varied from 45 to 330 c.c., the average for primiparas being 110 c.c. and for multiparas 65 c.c. As a safety measure, the level of cutaneous anesthesia must be constantly supervised, and should not rise above the umbilicus, as recently emphasized by Block and Rotstein.<sup>9</sup>

*Insertion of Needle.*—The equipment employed in this series was similar to that described by Edwards and Hingson. In our first 90 cases, the patient was placed in the knee-chest position during the in-

sersion of the caudal needle. After injection and attachment of the tubing, the patient was placed on her back with a pad over the needle, a small pillow beneath the knees, and a pad under the lumbar spine. This assisted in straightening the exaggerated lumbar lordosis as the muscle tension relaxed with the anesthesia and resulted in a reduction of post-partum backache. This technique, however, was discontinued since severe bending of the needle would occur at two places; one at the junction of the needle and the sacrococcygeal ligament and the other at the junction of the needle and the skin (Fig. 1). It was demonstrated that motion of the soft parts and fascia over the sacrum during the change from knee-chest to dorsal recumbent position caused this distortion of the needle and occasionally resulted in a withdrawal of the point to a level in the caudal canal where further injections were ineffective, thus making reinsertion of the needle necessary.

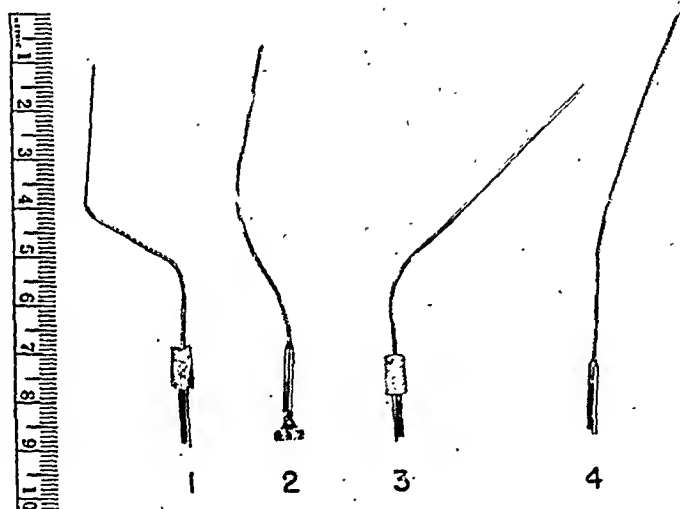


Fig. 1.—Photograph of needles obtained after injection into the sacral canal to induce caudal anesthesia. Numbers 1 and 2 show the bending which occurred when the patient was in the knee-chest position during insertion of the needle. Numbers 3 and 4 were obtained from patients who were lying prone when needle was inserted into the sacral canal.

Our present method is to place the patient in the prone position with a pillow under the thighs. The sacral hiatus is palpated, a skin wheal raised with metycaine solution, the sacrococcygeal ligament infiltrated, and the malleable stainless steel needle inserted. The needle is held in place with  $\frac{1}{4}$ -inch strips of adhesive tape extending from the left iliac crest down to and around the hub of the needle and up to the right iliac crest to form a "V." A split alcohol sponge is placed around the needle and the patient carefully turned to a modified Sims' position, where she remains. She is aided in changing from one side to the other with each subsequent injection. It is important to remember that 90 per cent of these patients are completely helpless as far as motor power in the lower extremities is concerned. This latter technique has been extremely satisfactory, causing little or no distortion and no breaking of the needle.

*Management Prior to Moving Patient to Delivery Room.*—When the cervix is completely dilated and the head is on the perineum, or when, in the judgment of the obstetrician in charge, the patient can be de-

livered within one hour without unwarranted interference, the caudal needle is removed and the patient then taken to the delivery room. In most instances, if injection has not been made during the preceding 20 minutes, 20 c.c. of metycaine are given before withdrawal of the needle. This technique is employed in primiparas and multiparas alike, and we should like to stress the point that moving the patient without first removing the caudal needle constitutes an unnecessary risk.

### Complications

A number of hazards are associated with this type of anesthesia and various precautions to prevent complications cannot be too strongly emphasized.

*Intravenous Injection of Anesthetic Agent.*—This may be prevented by careful aspiration before the metycaine is injected and by taking pains to turn the needle so that it does not ride along the anterior or posterior wall of the sacrum during insertion. In two instances in our series blood was aspirated after 5 to 10 c.c. of metycaine solution had been injected. Both patients suffered toxic reactions lasting 30 to 40 seconds, with clonic contractions of the muscles of the limbs and neck. Recovery, however, was rapid; the position of the needle was changed and the caudal anesthesia continued successfully.

*Breaking of the Needle.*—In four cases we experienced this complication and feel that the important responsible factors were: (1) employment of the knee-chest position for the preliminary injection; (2) allowing the patient to remain on her back; (3) moving her from the first-stage room to the delivery room without first removing the caudal needle; (4) repeated use of the same needle; and (5) the selection of German silver needles.

The use of the prone or lateral position during insertion of the needle, the employment of specially designed stainless steel malleable needles (Becton-Dickinson and Company), limiting the use of each needle to three times or less, and removing the needle before transporting the patient to the delivery room have eliminated this hazard almost completely.

*Infection.*—The prevention of infection at the site of injection requires extreme care in aseptic technique. The area selected must be prepared with suitable antiseptic agents and draped with sterile towels. The operator must wear sterile gloves, insert the needle, make the initial injection of 30 to 40 c.c. of metycaine and attach the tube from the metycaine bottle, tape the needle in place and then place a sterile split alcohol square about the hub of the needle. When the needle is removed, a sterile dressing must be placed over the puncture wound. One local infection occurred in our series, following surgical removal of a broken needle.

*Marked Fall in Blood Pressure.*—An alarming fall in blood pressure occurred in 5 cases. We believe this was due to marked vasodilatation in the anesthetized areas in patients with vasomotor instability. In these cases the blood pressure dropped to 70 mm. of mercury systolic or less; there was a remarkable decrease in pulse pressure, the pulse rate increased slightly, and the patients were pale and dry. This, however, is not an immediate complication, and the patients responded uniformly well to 3 or 4 minimums of neosynephrine given intramus-

cularly. In no instance did it necessitate discontinuing the anesthetic and no subsequent ill effects were noted in either mother or child.

*Toxic Symptoms.*—We observed that the speed of injection and the volume of the solution employed during the initial injection were important factors in the production of immediate toxic symptoms. Nausea and vomiting within 60 seconds of injection were encountered in 7 per cent of our cases. Some of these patients experienced brief bouts of nausea with each subsequent injection. It is the opinion of some authors that this manifestation, difficult as it may be to evaluate during pregnancy, occurs with no greater frequency in patients subjected to caudal anesthesia than in patients carried through labor by other methods. However, we failed to find a single patient who was willing to have the anesthetic discontinued because of this symptom.

Headaches and dizziness were occasional complaints. Syncope-like attacks were noted in two cases, and both were associated with definite evidence of intravenous injection of small amounts of the drug. One patient in the group not receiving premedication showed a very definite toxic reaction, as mentioned before, but it was not necessary to discontinue the anesthetic.

*Injection of Solution Into Subarachnoid Space.*—In more than 700 caudal injections, this accident, which may be serious by producing massive spinal anesthesia, was not encountered by us. Its prevention lies in careful aspiration before introducing the solution.

*Injury to Sacral Region.*—This complication was not experienced in this group, but it nevertheless is a potential hazard. An attempt was made to use ureteral catheters, as recommended by Adams et al.,<sup>6</sup> but we felt that the employment of larger needles increased the possibility of injury to the sacrum.

*Increase In Operative Deliveries.*—A large percentage of our series was delivered by operation, chiefly low forceps in vertex presentations. The explanation lies in the fact that with the absence of pain, it is difficult to obtain the cooperation of the patient in expelling the baby during the second stage. It should be noted, however, that in occiput posterior or transverse presentations, rotation with forceps was facilitated by caudal anesthesia, due to the complete relaxation of the perineum and pelvic musculature.

*Post-partum Complications.*—Post-partum conditions directly attributable to the caudal route of anesthesia were low back pain and increased irritability of the patients. In our experience, the low back pain occurred as soon as the anesthesia wore off. It lasted for 2 to 6 hours, and was present in about 12 per cent of our patients. This condition can be easily controlled with analgesic drugs and does not constitute a serious drawback to this method.

The increased irritability occurred most frequently in primiparas. It was not of serious consequence, usually consisting of bitter complaints about routine post-partum care and disappearing after 24 hours.

### Conclusions

1. Continuous caudal anesthesia was employed in 200 consecutive obstetric patients, in whom satisfactory results were obtained in 195 instances.

2. No obstetric complications which could be considered as contra-indicating the usage of this procedure were encountered by us.

3. The most important complications to look out for are the intravenous or subarachnoid injection of the drug, infection, breaking of the needle, fall in blood pressure, toxic manifestations, and trauma to the sacrum.

4. An increase in the number of operative deliveries was observed.

Our thanks are due to Eli Lilly and Company for a donation of metycaine, sodium amytal and seconal used in this study.

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## FINDINGS IN ROUTINE PELVIC EXAMINATIONS ON 1,998 WOMEN\*

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A SURVEY of the literature reveals a remarkable poverty of statistical information on the pelvic findings in groups of presumably healthy women. Most textbooks give the incidence of these findings only on the basis of general impressions and in the most general terms. The few available statistical studies in the literature of the past twenty years<sup>1-5</sup> for the most part deal with pelvic findings in hospital admissions, psychotic patients, and parous women. Only one study similar to the one being presented was found; that of Dunn in which 572 pelvic studies were done in the course of general physical examinations on supposedly healthy women from 20 to 65 years of age.<sup>6</sup> However, this group includes a much higher percentage of parous women if one may judge from the high incidence of cervical lacerations. The above study is, therefore, not strictly comparable to the one reported here.

The opportunity for this study was afforded by the active duty physical examinations, which were given all the apprentice seamen (WR) entering the Naval Reserve Midshipmen's School (WR) at Northampton, Massachusetts.

The physical examinations were given as soon as the women reported for active duty. Four classes are reported in this study, totaling 1,998 in all. Approximately 15 were examined per hour. The physical examination includes general body and neuropsychiatric examination, eye, ear, nose and throat examination, examination of heart and lungs, including pulse and blood pressure response to exercise, abdominal and vaginal or rectal examination, blood Kahn test and blood typing, followed by dental charting and photofluoroscopic examination of the chest. Each part of the physical examination is performed by a medical officer specializing in the particular branch of medicine involved. The pelvic and abdominal examinations reported here were all done by the authors. Pelvic examinations, either rectal or vaginal, are done with the patient in the usual lithotomy position. These are done irrespective of the menses. The abdomen is first palpated and the external genitalia are inspected. The state of the introitus determines whether vaginal or rectal examination is used. Rectal examination was necessary in 132

\*Approved for publication by the Bureau of Medicine and Surgery, U. S. Navy. The opinions presented are those of the writers and are not to be construed as official or reflecting the views of the Navy Department.



cases, or 6.6 per cent of the total cases. In 888 of the candidates a two-finger vaginal examination could be performed. Corresponding sizes of specula were used. Cervical cultures were taken on the first 1,468 women; on the last 530, they were taken only when indicated. These cultures are grown on proteose No. 3 and bacto-hemoglobin media, in Novy jars containing about 10 per cent carbon dioxide.

The composition of the group is shown by the following Table:

MARITAL STATUS	21 TO 25 YR.	26 TO 30 YR.	31 TO 40 YR.	41 TO 50 YR.	TOTAL
Total Exam.	944	583	422	49	1,998
Widow	4	3	5	3	15
Separated	1	1	1	0	3
Divorced	2	9	21	5	37
Married	30	30	49	13	122
Single	907	540	346	28	1,821

There are many factors which made this group a highly selected one. As can be seen from the above Table, there is a selection as to age and 91 per cent are single. Only 27 gave a history of any pregnancies.

All the women examined had a minimum of two years' college education; the great majority possessed at least a Bachelor's degree. The biggest factor of selection, however, is that all these women had a previous physical examination at their Navy Procurement Offices. In most cases, because of lack of facilities, these examinations did not include pelvic or rectal examinations. In the last group of cases examined in February, 1943, only 35.8 per cent had a previous pelvic examination. We know that prior to this time, very few Procurement Offices did pelvic examinations. It is estimated that only 5 per cent to 15 per cent of the previous groups were given this part of the examination before reporting for active duty.

About one-third of the girls examined at one of the large Procurement Offices failed to meet physical standards. We have no statistics available on the number disqualified for pelvic defects at that Naval activity.

The following are considered definitely disqualifying gynecologic defects according to the directive issued by the Bureau of Medicine and Surgery:

1. History of abnormality of the menstrual cycle, particularly disabling dysmenorrhea and amenorrhea unless determined to be the result of natural or artificial menopause.
2. History of chronic pelvic inflammation or an acute infectious pelvic disease.
3. Finding of congenital anomalies of clinical significance.
4. Conditions of pelvic organs which are considered likely to interfere with the performance of duty or to require surgical intervention.
5. Cervical culture found repeatedly positive for gonococci.

At the time of the physical examination the medical history is obtained. A detailed consideration of dysmenorrhea, amenorrhea and other abnormalities of the menstrual cycle would be valueless, because of the elimination of any candidate with any of these conditions by the Procurement Medical Officers. Also, the women are reluctant to admit readily the existence of disabling dysmenorrhea since they know it is disqualifying.

The following summary of gynecologic and obstetric histories as obtained by us is considered on the whole reliable:

Appendectomy	301
Supracervical hysterectomy	13
Myomectomy	1
Salpingectomy, bilateral	1
Salpingo-oophorectomy, unilateral	4
Oophorectomy, unilateral	10
bilateral	1
Cystectomy, ovarian	14
Resection of ovary	4
Dilatation and curettage	17
Suspension of uterus	12
Radium insertion for hemorrhage	1
Adhesions, lysis of	2
Sympathectomy, presacral	1
Polypectomy, cervical	1
Inguinal hernia repair	1
Meckel's diverticulum	1
Exploratory laparotomy	2
Vaginal cyst removed	1
Excision, Bartholin's cyst	1
Menopause	3
Metrorrhagia	2
Pregnancies	
Full-term delivery	8
Stillbirth	1
Premature stillbirth	1
Miscarriage—3 months	11
3½ months	1
6 months	2
Ectopic pregnancies	3

For purpose of study, we have divided the women into age groups of 20 to 25, 26 to 30, 31 to 40, 41 to 50 years. There were 1,279 women with normal pelvic findings. The defects listed below were found in the remaining 719.

DEFECT	20 TO 25		26 TO 30		31 TO 40		41 TO 50		TOTAL	
	No. 1,000		No. 1,000		No. 1,000		No. 1,000		No. 1,000	
	No.	Per	No.	Per	No.	Per	No.	Per	No.	Per
TOTAL CASES	945		583		421		49		1,998	
Pregnancy	3	3.2	0	0.0	1	2.4	0	0.0	4	2.0
Perineal lacerations	0	0.0	1	1.7	3	7.1	1	20.4	5	2.5
Bartholin cysts	0	0.0	1	1.7	1	2.4	0	0.0	2	1.0
Rectocele	0	0.0	0	0.0	0	0.0	1	20.4	1	0.5
Partial septum of vagina	1	1.1	1	1.7	0	0.0	0	0.0	2	1.0
Vaginitis—senile	0	0.0	0	0.0	1	2.4	3	61.2	4	2.0
Vulvovaginitis undifferentiated	5	5.3	10	17.2	6	14.3	2	40.8	23	11.5

DEFECT	20 TO 25		26 TO 30		31 TO 40		41 TO 50		TOTAL	
	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000
Cervix erosion										
Slight	68	72.0	39	66.9	16	38.0	3	61.2	126	63.1
Moderate	17	18.0	19	32.6	16	38.0	1	20.4	53	26.5
Cervicitis										
Moderate	9	9.5	8	13.7	3	7.1	1	20.4	21	10.5
Marked	1	1.1	1	1.7	0	0.0	0	0.0	2	1.0
Cystic	7	7.4	9	15.4	13	30.9	1	20.4	30	15.0
Endocervicitis	5	5.3	1	1.7	6	14.3	0	0.0	12	6.0
Total cervical erosions and cervicitis	107	113.2	77	132.1	54	128.3	6	122.4	244	122.1
Healed lacerations	2	2.1	3	5.1	6	14.3	3	61.2	14	7.0
Polyps	0	0.0	1	1.7	5	11.9	2	40.8	8	4.0
Cervical cultures positive for gonorrhea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Uterus										
Infantile	8	8.5	4	6.9	1	2.4	0	0.0	13	6.5
Bicornuate	0	0.0	0	0.0	2	4.8	0	0.0	2	1.0
Enlarged, firm	3	3.2	3	5.1	11	26.1	1	20.4	18	9.0
Fibromyomas										
Intramural	0	0.0	5	8.6	12	28.5	10	204.1	27	13.5
Subserous	0	0.0	2	3.4	6	14.3	2	40.8	10	5.0
Total fibromyomas	0	0.0	7	12.0	18	42.8	12	244.9	37	18.5
Total fibromyomas plus enlarged, firm uteri	3	3.2	10	17.2	29	67.9	13	265.3	55	27.5
Retrocessed	12	12.7	11	18.9	7	16.6	0	0.0	30	15.0
Retropositions										
1st degree	40	42.3	21	36.0	20	47.5	2	40.8	83	41.5
2nd degree	42	44.4	39	66.9	23	54.6	5	102.0	99	49.5
3rd degree	16	16.9	16	27.4	16	38.0	1	20.4	49	24.5
Lateral displacement										
Right	4	4.2	1	1.7	3	7.1	1	20.4	9	4.5
Left	6	6.3	2	3.4	1	2.4	0	0.0	9	4.5
Prolapsus, 1st degree	1	1.1	1	1.7	3	7.1	1	20.4	6	3.0
Total malpositions	119	125.9	90	154.4	73	173.2	10	204.1	282	141.1
Adnexae										
Ovarian cysts	3	3.2	3	5.1	3	7.1	0	0.0	9	4.5
Cystic ovaries										
Right	7	7.4	7	12.0	2	4.8	0	0.0	16	8.0
Left	18	19.1	4	6.9	4	9.5	0	0.0	26	13.0
Bilateral prolapsed cystic ovaries	5	5.3	0	0.0	1	2.4	0	0.0	6	3.0
Total cystic ovaries	30	31.8	11	18.9	7	16.6	0	0.0	48	24.0
Induration of adnexa										
Right	2	2.1	2	3.4	1	2.4	1	20.4	6	3.0
Left	5	5.3	3	5.1	1	2.4	0	0.0	9	4.5
Bilateral	1	1.1	0	0.0	0	0.0	1	20.4	2	1.0
Total induration of adnexa	8	8.5	5	8.6	2	4.8	2	40.8	17	8.5
Pediculi pubis	1	1.1	0	0.0	0	0.0	0	0.0	1	0.5
Furuncle of perineum	0	0.0	1	1.7	0	0.0	0	0.0	1	0.5
Skenitis culture negative for gonococcus	0	0.0	0	0.0	0	0.0	1	20.4	1	0.5
Congenital opening of urethra on labia minora	0	0.0	1	1.7	0	0.0	0	0.0	1	0.5

Of the preceding findings, the following were disqualifying:

Pregnancies	4
Large bilateral cystic ovaries	1
Ovarian cysts	6
Metrorrhagia	2
Fibromyomas	4

### Discussion

The classification used is, of course, a purely clinical one. There was no opportunity to investigate the etiology of minor defects. Some of the terms employed may require some explanation which will be given in the course of the discussion.

Because of the lack of laboratory facilities, no bacteriological investigation of the cases of vaginitis could be made; therefore, only two classifications were made, namely, senile vaginitis and undifferentiated vulvovaginitis.

In the classification of cervical pathology, standard clinical terminology was used. Since the classification is made on clinical impressions, the clinical entities overlap each other. Therefore, the most significant opinion as to incidence should be based on the total cervical erosions and cervicitis. No cervical biopsies were taken. However, no cervical pathology suggestive of carcinoma was found. Here again, one should realize that we are dealing with nulliparous women predominantly.

One of the two bicornuate uteri was previously diagnosed by x-ray. The other is a clinical diagnosis but nevertheless definitely confirmed. The two cases of bicornuate uteri plus the two cases of septate vagina and congenital opening of urethra make a total of five cases of congenital anomalies, or an incidence of 2.5 per 1,000. The term "enlarged, firm uterus" is a purely descriptive one. We found a number of uteri that varied from one and a half to two times the normal size. This entity was more common in those of the fourth and fifth decades. Since the incidence follows that of fibromyomas, the authors are of the opinion that this clinical entity is related to fibromyomas or fibrosis uteri. For this reason, we have added them to our incidence of fibromyomas. The authors realize that the terms "intramural" and "subserous" are not pathologically accurate and represent only the predominant clinical findings in cases of multiple fibromyomas. The fibromyomas varied in size from those two centimeters in diameter to one which extended almost to the umbilicus. Only four of the 37 fibromyomas were of sufficient size or clinical significance to require surgical intervention. These women were disqualified. Fourteen women gave a history of hysterectomy or myomectomy for fibromyomas. This number added to the 55 found in this study gives an incidence of 34.5 cases per thousand examined in this group.

The classification of retroposition was used instead of dividing the cases into retroflexions and retroversions. The authors felt that the difference would be too easily missed in the course of the quick pelvic

examination and, therefore, the term "retroposition" would be more accurate. Twelve women stated that they had had suspensions of the uterus. Ten of these stated that dysmenorrhea was the indication for this operation.

The association of erosion or cervicitis and retroposition is often mentioned. Thirteen and nine-tenths per cent of the 267 women having retroversion, retroflexion or retrocession of the uterus had some degree of cervicitis or erosion. However, an incidence of 13.8 was found in the total group in which the cervix was visualized. There is, therefore, no correlation between cervical erosion or cervicitis and retroposition.

Eighteen cases of lateral displacement were found in the entire group. No cause for this displacement could be discovered in eleven of these cases. In two cases cystic ovaries had pulled the uterus laterally; ovarian cysts accounted for two of the cases; and induration of the adnexa for three others.

The ovarian cysts varied in size from one small one, 3 centimeters in diameter, to one 10 centimeters in diameter. Six of the nine cases of ovarian cysts were large enough to be considered operable and, therefore, disqualifying. Sixteen women gave a history of having had one or both ovaries removed. Therefore, 22 women, 11.0 per thousand of the 1,998 examined, had had surgery or required surgery for ovarian pathology at the time of the examination. One of the patients having cystic ovaries was disqualified because both were over three times the normal size. They were prolapsed and exquisitely tender.

Of the sixteen cases of induration of the adnexa, five gave no history of previous pelvic disease or operation. Twelve had had operative procedures which would account for the induration. Two of these operations were performed because of pelvic inflammatory disease.

Because of the small number of married or parous women, no correlation of pathology with these factors was attempted. The numbers in the higher age groups were small, but the authors considered them adequate to give a rough correlation of pathology with age. The correlation of healed perineal and cervical lacerations is an obvious one. Similarly, there is a definite increase in the incidence of senile vaginitis. However, undifferentiated vulvovaginitis also increased with age. Cervicitis had, however, no significant incidence variation per decade of life. The number of cervical polyps discovered was small, but here again there is a definite increase in the older age groups. The sharp correlation of the incidence of fibromyomas with age is the expected one. First-degree prolapsus uteri and total malpositions also increase with the age.

### Summary

Routine pelvic examinations were done on a group of 1,998 presumably healthy, white women in the younger age levels. Approxi-

mately one-third of the women had some type of gynecologic condition predominantly of minor nature. The incidence of major pathology as presented here errs on the side of conservatism since some 10 per cent to 15 per cent of the women had previous pelvic examinations at the Procurement Offices, and some cases were undoubtedly eliminated because of major pelvic pathology. Despite this, the figures on incidence of fibromyomas uteri and ovarian cysts are higher, in the authors' opinion, than would be expected. The total incidence of fibromyomas was 27.5 per thousand, which is higher than one would expect in a predominantly young group. Nine ovarian cysts were found, six of which were large enough to require operation.

Naturally the incidence of minor pathology would not be affected by any elimination due to previous pelvic examinations. The incidence of vaginitis per thousand was 13.5; total cervical erosions and cervicitis 122.1; cervical polyps 4.0; total malpositions 141.1; total cystic ovaries 24.0; and induration of the adnexa 8.5. These figures should represent the incidence per thousand in any similar group.

Of the 1,998 women examined, ten were candidates for major surgery. Two cases, because of a history of metrorrhagia, were rejected and presumably would undergo diagnostic curettage. Eight cases required removal of cervical polyps. Twenty-seven had vaginitis. Two hundred and forty-four had cervical erosions or cervicitis. According to current gynecologic practice, treatment is advisable in these cases. This large group requiring treatment (291 out of 1,998) once again emphasizes the need for careful routine pelvic examinations.

### Conclusions

1. There is an obvious need for routine pelvic examinations not only in women of the menopausal age but also in younger women.
2. Vaginal examinations are possible regardless of marital status in all but a very small minority.

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## ✓ A COMBINED EXTRAUTERINE AND INTRAUTERINE PREGNANCY

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COMBINED extrauterine and intrauterine pregnancy, although infrequent, is by no means rare as once was thought. These cases are always of interest because of their diagnostic difficulties and resulting high mortality rate. Gemmell and Murray<sup>2</sup> in their analysis of 217 cases, computed a mortality rate of 20.7 per cent for the entire series, or 14.4 per cent if those cases were excluded which were diagnosed only at autopsy without any previous treatment. It is the purpose of this report to point out that since this condition is occasionally encountered and since the mortality rate is high, the possibility of a combined pregnancy should be kept in mind in a differential diagnosis.

The extrauterine rather than the intrauterine pregnancy is the dangerous factor. Frequently, the diagnosis of extrauterine pregnancy is made, but the patient will abort (as in the case to be reported) via vagina, and one is misled into the false diagnosis of incomplete or completed abortion with infection or uterine injury. In other cases, the diagnosis of extrauterine pregnancy is made with some reservation and upon doing a diagnostic curettage and recovering placental tissue, the extrauterine pregnancy is overlooked until later, sometimes too late.

In computing the number of cases to date, the literature is confusing, overlapping and incomplete. Duverney,<sup>1</sup> in 1708, is given credit for reporting the first case, found in a post-mortem examination. However, without much doubt, combined pregnancies must have occurred prior to this date. In spite of the supposedly careful compilations by other reviewers, cases have been omitted by them. There must be many unreported cases and many journals unavailable to most authors, so that an accurate collection of cases is impossible. Mitra<sup>11</sup> and Ludwig<sup>8</sup> both reviewed the recent literature in 1940, yet in only a few instances did their cases overlap.

Novak<sup>1</sup> in 1926 made an exhaustive study from 1708 to 1926 quoting Duverney, Zinke, Simpson and Neugebauer. He differentiated between compound and combined intrauterine and extrauterine pregnancies. The former was believed to be more frequent and referred to an extrauterine pregnancy with spontaneous resolution or lithopedion formation and subsequent intrauterine pregnancy. The latter he considered rarer and referred to both pregnancies occurring at the same time. His total of cases, including 32 from recent literature and two of his own, up to 1926, was 276. Gemmell and Murray<sup>2</sup> made "a limited survey of the literature" and reported 217 cases up to 1931, including two cases of their own and two cases reported in 1932. They gave recognition to Novak's article<sup>1</sup> and the cited 276 cases. They believed some of the cases were not combined, but twin pregnancies in the tubes or in two horns of bicornuate uteri. They themselves reported only those cases in which they personally studied the original article or an abstract of it. Mathieu<sup>3</sup> reviewed the literature through 1936 and added 57 cases which had not been reported by Gemmell

and Murray or Novak, thus making the total either 274 (if added to Gemmell's figure) or 333 (if added to Novak's). Sloat and Peterson<sup>4</sup> tabulated the cases added by Novak, Stein and Gemmell, and found that there were 64 new cases which could be added to Neugebauer's 244 cases cited in 1913. They added 15 cases from the literature which had not appeared in previous tabulations in addition to one case of their own, bringing a revised total of 324 up until 1936. However, in December, 1939, Rosenthal<sup>7</sup> went back to Heffernan's review in 1935, of 277 cases and added 9 cases which he found since in the literature (without enumerating them) plus one personal case, totaling 287 cases. Ludwig<sup>8</sup> reviewed 17 cases in the literature since Mathieu,<sup>3</sup> plus 3 cases of his own and adding them to Mathieu's brought the total through 1938, to 294 (using Gemmell's figures) or 353 (using Novak's). Mitra<sup>11</sup> also reviewed the literature from Duverney and stated that up to 1940, there were only 304 cases cited, including two of his own. The recent literature has been reviewed for this report, and 15 cases not included by Ludwig, and 18 not included by Mitra have been discovered.<sup>4-17</sup> This brings the total to either 322 (by adding to the compilation of Mitra) or 309 to 368 (by adding to the estimate of Ludwig).

The case to be reported is interesting because of the possibilities the patient presented in a different diagnosis. It is the first instance of this condition encountered in Bellevue Hospital since 1918.

R. M. (38747-43), a 28-year-old, married, colored female, gravida ii, para ii, was admitted to the gynecological service at 11:00 P.M. on 8/17/43. Her chief complaint was abdominal pain. Her menstrual periods had always been regular, her last menses having occurred 6/17/43. She had missed her July period, but had no subjective signs or symptoms of pregnancy. Approximately two weeks before her admission to the hospital, she began to pass small blood clots *per vaginam* with gradual increase in bleeding and then subsidence, so that on admission she had merely pinkish spotting. About four days before her admission, following an indefinite period of generalized abdominal tenderness, the patient developed sharp intermittent pains in both lower quadrants. On admission, pain was localized to the right lower quadrant with transmission to the rectum. She suffered from nausea, but had not vomited. The history of the background of the patient supplied two pertinent facts: (1) Both the patient's mother and mother-in-law had twin pregnancies. (2) In 1941, patient was treated for "inflammation" in her pelvis by bed rest for one month.

*Physical Examination.*—Blood pressure 120/80, pulse 90, respirations 20, temperature 99° F. Patient was a moderately obese, colored female of stated age, who appeared uncomfortable, but not in acute distress. General physical examination was essentially negative. Breasts showed Montgomery's tubercles to be present, but no secretion could be demonstrated. The abdomen was full and soft with some resistance to light palpation in the right lower quadrant. There was tenderness to deep palpation over entire abdomen with rebound tenderness, being most marked in the right lower quadrant. The abdomen was tympanitic throughout. Pelvic examination revealed a relaxed two fingers' introitus. The cervix was irregular, soft, tender on motion, pointing in the axis of the vagina, and the external os admitting a finger tip. The uterus was enlarged to about the size of a 3 months' pregnancy, fixed, very tender and in midposition. The adnexa showed marked tenderness, and on the left side, a flattened 4 by 8 cm., firm, thickened mass which ex-



tended into the cul-de-sac. Speculum examination revealed a positive Chadwick sign, old lateral laceration of the cervix with ectropion and a light-brown dirty discharge. Rectovaginal examination confirmed the above findings.

### *Laboratory Data:*

W.B.C.	10,400
R.B.C.	4,800,000
Hgb.	14 Gm.
Sedimentation rate	25 min. (18 mm.)
Urinalysis, Specific gravity 1.033, Alkaline reaction, no albumin, 1+ sugar and rare W.B.C. per high power field.	

A tentative diagnosis of left tubal pregnancy with tubal abortion was made. However, because of the large size of the uterus, rapid sedimentation rate and history of pelvic inflammation, the possibility of intrauterine pregnancy with bilateral chronic adnexal disease was considered. She was seen 12 hours later by an attending physician who made the diagnosis of threatened uterine abortion and advised expectant treatment.

On August 22, 1943, at 6:45 P.M. (5 days after her admission) patient spontaneously aborted a fetus about 8 weeks in size, together with placental tissue. Patient's temperature rose to 103° F., and remained elevated for the next six days. Lower abdominal pain became increasingly severe. During this time, five pelvic examinations were made by various attending physicians. The following diagnoses were considered: Fibromyomata uteri, tuboovarian abscess, infected ovarian cyst, acute degeneration of a fibroid.

On 9/1/43, the mass which had been felt previously in the cul-de-sac was found on examination to have disappeared and an immediate laparotomy was advised. Laparotomy revealed a ruptured left tubal pregnancy. A left salpingectomy was performed. Since the accumulated blood in the cul-de-sac had a definite colon odor, the abdomen was drained. Except for considerable discharge from the lower angle of the wound, she had an uneventful recovery.

### *Pathological Report:*

(a) Material expelled from the uterus (Accession No. 2393-1943). Degenerating decidua and placental tissue.

(b) Mass removed at laparotomy (Accession No. 2240-1943).

Left tubal pregnancy with external rupture.

Chronic follicular salpingitis.

In both specimens, the placental tissue showed relatively little degeneration and appeared quite similar, showing without doubt, that the pregnancies were simultaneous or combined rather than sequential or compound.

### **Comment**

Combined extrauterine and intrauterine pregnancies are not as rare as is commonly believed. A review of the literature up until 1942 reveals the number of such cases reported to total between 309 and 368, the actual number probably being much greater. Since this unusual form of binovular twin pregnancy is not rare, it should be borne in mind whenever a patient who appears to have an intrauterine pregnancy suffers from unusual pain and bleeding during the early months of

gestation. The possibility of an associated tubal pregnancy is greatly increased if a tender adnexal mass can also be made out. A family history disclosing a predisposition to multiple pregnancy or a previous history of adnexal disease may be of some value.

A review of the literature shows that the most favorable outcome results when the ectopic pregnancy undergoes rupture without disturbing the uterine gestation. In such cases, the ectopic pregnancy manifests itself first, is recognized and promptly brought to surgery. In an analysis by Morse<sup>6</sup> 40 per cent of combined pregnancies followed such a course, and the intrauterine pregnancy proceeded normally to term.

Gemmell and Murray<sup>2</sup> subdivided their cases into definite groups and computed the mortality rate in each such group. Their results were as follows:

1. Cases discovered at autopsy.	16 cases	16 deaths	100%
2. Cases discovered after delivery of uterine pregnancy.	41 cases	6 deaths	14.6%
3. Cases discovered during the second half of pregnancy or during labor.	20 cases	7 deaths	35%
4. Cases discovered during the first half of pregnancy after abortion of the uterine pregnancy.	47 cases	7 deaths	15%
5. Cases discovered during the first half of pregnancy before abortion of the uterine pregnancy.	93 cases	9 deaths	9.7%

From this study, it appears the group of cases which has yielded the greatest mortality is marked by the preliminary abortion, delivery, or discovery of the uterine pregnancy followed by rupture of the ectopic pregnancy. The mortality following this sequence of events has been high and in the neighborhood of 20 per cent. It is to this group that the new case reported belongs. Superficially this case resembles a post-abortion infection. Only repeated examinations and the discovery of the disappearance of the pelvic mass led to laparotomy and the revelation of the true diagnosis.

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## THE RESULTS OF SURGICAL CASTRATION IN WOMEN UNDER FORTY

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THE gynecologist, in operating upon women under forty, especially those suffering from chronic adnexal disease, often allows his choice of operative procedure to be influenced by a desire to preserve ovarian function, even though the question of future pregnancy is not involved. Thus, he may choose a less radical procedure and risks the possibility of the recurrence of symptoms because moderately diseased adnexa have not been removed.

What is the actual hazard of surgical castration in women under forty? In an effort to answer this question, a study of the results of surgical castration in women under forty was started at Bellevue Hospital in 1940. The scope of the investigation was to be wide enough to include answers to the following:

1. How often and how soon does the menopausal syndrome follow surgical castration?
2. How severe is the menopausal syndrome?
3. How long does the menopausal syndrome last?
4. What is the influence of surgical castration on libido?
5. How often does surgical castration precipitate the appearance of any other constitutional disease?
6. What is the influence of surgical castration on blood pressure?

At the outset, certain criteria were established:

1. All patients were to be under forty.
2. No woman was to have suffered symptoms of a spontaneous menopause before operation.
3. All cases were to be complete surgical castrates.
4. The minimal period of postoperative observation was to be three months.
5. No patient was to receive estrogenic therapy before a minimal period of six months of observation.
6. Estrogenic therapy was to be administered only if symptoms were not controlled by mild sedatives.
7. 150 mg. Hg systolic and 90 mg. Hg diastolic pressure was to be considered the upper limit of normal blood pressure.
8. A minimal fluctuation of 20 mg. Hg systolic and 15 mg. Hg diastolic pressure was required before a change in blood pressure was said to have occurred.

In the three years that this study has been carried on, 41 cases have been accumulated subscribing to the above prerequisites. Thirty-six of these women were colored and 5 white. The preponderance of colored patients was due to the fact that the most common reason for total cas-

tration was chronic adnexal disease, a much more prevalent affliction in the colored race at Bellevue Hospital.

The age group of the patients is shown in Table I. It will be noted that 71 per cent were under 35.

TABLE I. AGE GROUP

A. Less than 20	1	} 71%
B. 20 to 25	4	
C. 25 to 30	6	
D. 30 to 35	18	
E. 35 to 40	12	29%

It will be noted in Table II that 54 per cent of the patients were observed longer than a year.

TABLE II. DURATION OF OBSERVATION

From 3 to 6 months	6	} 54%
From 6 to 12 months	13	
From 12 to 18 months	10	
From 18 to 24 months	9	
From 24 to 36 months	3	

Thirty-five or 85 per cent of the cases had a precipitate menopause appearing immediately after castration. Six or 15 per cent had no symptoms whatsoever. The nature and severity of symptoms in the order of frequency are recorded in Table III.

TABLE III. NATURE AND SEVERITY OF MENOPAUSAL SYMPTOMS

	NONE	OCCASIONAL	MODERATE FREQUENCY	DISTRESSING
Flushes	16	21	7	7
Headaches	23	18	0	0
Insomnia	26	14	1	0
Dizziness	29	11	1	0
Arthralgia	33	8	0	0

As to libido, 36 or 88 per cent of these patients found no change. Three or 7 per cent found their libido diminished; whereas 2 or 5 per cent actually experienced an increase in libido.

It will be observed in Table IV that 50 per cent of the cases had their symptoms last less than 6 months, 75 per cent less than a year.

TABLE IV. DURATION OF MENOPAUSAL SYMPTOMS

A. Less than 3 months	10 or 25%
B. 3 to 6 months	11 or 25%
C. 6 to 12 months	10 or 25%
D. 12 to 24 months	6 or 15%
E. 24 to 36 months	4 or 10%

As far as the severity of symptoms was concerned, in only one case were menopausal symptoms sufficiently severe to be uncontrolled by barbiturates and to require estrogenic therapy. Thirty or 75 per cent were controlled with barbiturates; whereas 10 or almost 25 per cent required no therapy at all.

No patient in this series developed a constitutional disease, such as diabetes, arthritis, or thyrotoxicosis, following surgical castration. Only one woman of 35 developed a slight elevation of blood pressure. Her preoperative pressure was 138 mg. Hg systolic and 86 mg. Hg diastolic. Seen in the return clinic four weeks following her operation, her blood pressure was 164 mg. Hg systolic and 96 mg. Hg diastolic. It maintained approximately this level for the 4 months during which she was observed. Her menopausal symptoms were not severe and were controlled with barbiturates. Symptom-free, she failed to return for further checkup. This case merely points out the necessity of the continuation of such a study in a number of clinics so that many more cases can be accumulated and the incidence of hypertension following castration can be more accurately compared with the incidence of essential hypertension occurring in women of the same age who have not been castrated. The precipitate appearance of hypertension following the operation is not necessarily proof of its direct relationship.

### Summary and Conclusions

From the careful observation and study of this small group of patients it can be assumed that:

1. Surgical castration results in the abrupt onset of the menopausal syndrome in 85 per cent of cases. In a minority (15 per cent) no evidence of this syndrome appears.

2. In the vast majority of instances the menopausal symptoms are not severe and do not require estrogenic therapy, being easily controlled by barbiturates.

3. The duration of such symptoms is usually brief; in 50 per cent of the patients being less than 6 months, and in 75 per cent, less than a year.

4. Libido is usually uninfluenced by this procedure, being diminished in 7 per cent, while in 5 per cent the patient actually experienced an increase in libido.

5. In no instance, did surgical castration precipitate the appearance of any constitutional disease.

6. In only one instance was surgical castration followed by evidence of hypertension. The relationship of this sequence is considered to be highly doubtful.

7. It is believed that the distressing aftereffects of surgical castration in relatively young women for justifiable indications are frequently exaggerated.

## TREATMENT WITH PENICILLIN AFTER THE FAILURE OF SULFA DRUGS IN A CASE OF VAGINAL PLASTIC FOLLOWED BY BLOOD STREAM INFECTION\*

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MRS. B. I., aged 49, was seen in consultation at a private hospital. The history was as follows: Gravida ii, para ii, suffered from rheumatic endocarditis, arteriosclerosis, hypertension and menopause. The family physician reports that her blood pressure was 212/98. Under treatment her blood pressure dropped to 148/78 and palpitation was relieved, but the protruding of the vagina, which could not be helped with a pessary, caused the family physician to refer her to a surgeon who did a repair of the enterocele. The record at the private hospital described the operation as a "Manchester," and further stated that following the operation the patient was well for a few days. Then her temperature rose to 105° F. She received an intravenous injection of glucose with sulfathiazole, temperature dropped to normal and remained so for a few days. Then the temperature rose again and the treatment was repeated with a similar reaction.

When the patient was first seen she was a very thin, hypertensive individual with slight vaginal oozing and a septic temperature curve. Vitamin K and transfusion were recommended for the bleeding. This treatment acted most favorably and after the temperature had been normal for four days, the patient was discharged from the institution. Shortly after her return home the high temperatures recurred and the patient seemed sicker than ever. Then at the request of the family and of the family doctor and the operating surgeon, she was admitted to the gynecological wards of the Lenox Hill Hospital. The history taken at the time of her admission, though most complete, adds nothing of importance to the story as here told.

On admission to the Lenox Hill she was acutely ill and had a temperature of 103.6° F., which rose the next day with a chill to 106.6° F. Careful examination revealed no cause for the temperature and the general condition, but the laboratory reported *Streptococcus hemolyticus* from blood culture on two successive examinations. We then naturally thought that we were pretty much at the end of our troubles and that we could cure the patient promptly. Therefore, sulfadiazine was started intravenously and by mouth and was pushed to the point where the sulfadiazine level in the blood was 66.6 mg. and the patient was passing only about 300 c.c. of urine though taking 2,500 c.c. by mouth and infusion, and sulfadiazine crystals were present in the urine. Despite this heroic treatment very little was gained. During the course of the illness five or six small transfusions were given. On the twentieth day after admission to the hospital, when the temperature was still between 103° F., and 105° F., the first dose of penicillin was given and continued as follows:

\*Read at the meeting of the New York Academy of Medicine, Section on Gynecology and Obstetrics, October 26, 1943.

Forty thousand Oxford units daily for 7 days; the first 24 hours in a continuous intravenous saline drip and then intramuscular injections every 3 hours. The eighth to the eleventh day the dose was cut to 30,000 Oxford units daily, 5,000 given every 4 hours. Medication was given for 11 days with a total of 370,000 Oxford units.

In the first 36 hours the patient showed tremendous clinical improvement and the blood culture then gradually became sterile. On the forty-eighth day after admission to the hospital the patient was discharged seemingly cured, having had normal temperature for 14 days and a pulse that had gradually come down to normal.

During her stay at the hospital her basal metabolism rate was shown to be plus 6 per cent and the electrocardiograph reading was within normal limits. X-rays of the chest and abdomen were negative. The urine which at first showed bacteria and pus, hyaline and granular casts, also gradually improved under the treatment. When the patient was seen on October 6, she had a blood pressure of 192/106, her weight was 97½ pounds, which was about ten pounds under her normal, and the urine was negative. Except for general weakness everything was then satisfactory.

812 PARK AVENUE



## ABDOMINAL PREGNANCY REQUIRING SECONDARY REMOVAL OF THE PLACENTA

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FEW patients with abdominal pregnancy require subsequent surgical removal of the placenta. In the absence of infection, it is usually agreed that the placenta left in the abdomen will become absorbed.<sup>1, 2</sup>

That this does not always occur is shown by the following report and two other cases found in the English literature of the past ten years. In 1940, Nicodemus and Carrigg<sup>4</sup> reported a case in which the placenta did not absorb but suppurated and became walled off from the peritoneal cavity. The placenta was subsequently removed from an abscess wall which localized in the right upper quadrant of the abdomen. The patient recovered. In 1940, Lull<sup>3</sup> reported a case of abdominal pregnancy in which the placenta did not absorb. Two months after the original laparotomy it was necessary to remove part of the large hemorrhagic cyst which had formed. The remainder of the cyst was closely adherent to the intestine and was marsupialized and packed. The patient made a good recovery.

Symptoms associated with nonsuppurative encapsulation of a retained abdominal placenta are recorded in the following report.

J. J., colored, aged 22, gravida ii, para i, was admitted to Gallinger Municipal Hospital on April 21, 1942, complaining of cramp-like pains in the upper abdomen. Her last normal menstrual period began November 25, 1941. This was followed by slight bleeding in December and January. For two weeks, she had experienced sharp, intermittent abdominal pain which had become quite severe on the day of admission. She had had no fainting or shoulder pain. Past history included an uncomplicated delivery of a full-term, living infant in 1938, and acute salpingitis in November, 1940.

On admission temperature was 98.6° F., pulse 112, respirations 20, and blood pressure 120/75. The abdomen was enlarged and diffusely tender. Fetal movements could be felt which coincided with the attacks of pain. Fetal heart sounds were present. The fundus of the uterus extended to the level of the umbilicus. The right round ligament was palpable. A firm, tender, ballotable mass beneath the left costal margin seemed to be attached to the fundus. The cervix was soft, blue, and closed. The cul-de-sac was clear.

A soft tissue x-ray of the abdomen showed a fetus of approximately seven months' gestation. It occupied the left side of the abdomen from the iliac crest to just beneath the diaphragm. There was no evidence of a uterine wall surrounding the fetus.

The blood Kahn and urinalysis were negative. Blood count showed hemoglobin of 88 per cent, erythrocytes 4,400,000, and leucocytes 10,600.

A preoperative diagnosis of abdominal pregnancy with ruptured membranes was made on April 22, 1942. A laparotomy was performed in which the uterus was found to be symmetrical, soft, and enlarged to the size of a four months' pregnancy. The right tube was not identified, but a mass 8 cm. in diameter, presumably a hematoma, was found in the right broad ligament. The placenta was firmly attached to the fundus of the uterus, to several loops of intestine, and to the mesentery. The



membranes had ruptured and the fetus was lying free in the abdominal cavity underneath the dome of the left diaphragm. A living 2 pound 15 ounce (1,333 grams) infant was delivered. The cord was ligated close to the placenta and cut. There was no appreciable bleeding. For fear of provoking hemorrhage and injuring the bowel, the placenta was left in situ and the abdomen closed. The infant died twelve hours after delivery.

The patient's postoperative course was afebrile. She was discharged on the twenty-seventh postoperative day.

On June 2, 1942, she complained of swelling and occasional pain in the abdomen. The abdominal sear was well healed. The body of the uterus was anterior and enlarged to twice normal size. A cystic mass, 10 cm. in diameter, rested on the right side of the fundus of the uterus.

On June 17, 1942, the patient was readmitted to the hospital complaining of severe lower abdominal pain, and vomiting of twelve hours' duration. Physical findings had not changed since the last clinic visit. The patient continued to vomit, developed shoulder pain, pallor, shifting dullness in the abdomen, and an acute anemia. She showed no signs of shock. Intra-abdominal bleeding from an old retained placenta was considered. She was treated with bed rest, sedation, blood transfusions, and supplemental vitamins. The acute symptoms subsided within a few days. A quantitative Aschheim-Zondek test was negative in all dilutions. She was discharged improved on her fourteenth hospital day.

She returned five days later with recurrent severe epigastric pain. These attacks continued to recur at irregular intervals. The mass in the abdomen seemed to be enlarging. On July 30, 1942, approximately three months after the delivery of the baby, an exploratory laparotomy was done. The lower abdomen was filled by a large cystic mass approximately 20 cm. in diameter. The cyst was completely encapsulated by the omentum and small and large bowel. The appendix was closely adherent to the cyst. The liver was not involved. The omentum was freed from the anterior wall of the cyst. In freeing several loops of bowel, incision was carried through the posterior wall of the cyst allowing approximately 500 c.c. of rust-colored fluid to escape. As soon as the bowel and the omentum were freed, the anatomical pathology became apparent. The uterus was small, anterior and well involuted. The placenta was closely adherent to the posterior and superior wall of the uterus. The bulbous, fimbriated end of the left tube and the ovary were attached to the cyst wall. The right tube was intimately attached to the cyst. The right infundibulopelvic ligament was hypertrophied and contained greatly enlarged vessels which had evidently been the source of the major blood supply to the placenta. A supracervical hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The abdomen was closed without drainage.

The patient's postoperative course was uncomplicated. She was discharged on the thirteenth postoperative day.

Since her discharge from the hospital on August 12, 1942, the patient has gained 27 pounds. Hot flushes have been entirely relieved by estrogen substitution therapy. On January 28, 1943, six months after removal of the placenta, examination showed that the abdomen was well healed; the cervix was clean, well supported and closed; pelvis was entirely free of masses or tenderness.

### Summary

A case of abdominal pregnancy requiring secondary removal of the placenta is reported. It is of interest that the placenta did not absorb or suppurate, but became encapsulated by the bowel and omentum. Subsequent abdominal symptoms became so severe that surgical intervention was undertaken. These were completely relieved by secondary removal of the placenta.

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# Editorial

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## A Friendly Gesture

A RECENT announcement which should prove of interest to American obstetricians and gynecologists comes from England. It relates to the endowment of a lectureship by an anonymous donor, a Fellow of the Royal College of Obstetricians and Gynecologists. The interest from a fund of one thousand guineas is to be devoted to a lecture every second year alternately by a member of the Royal College on the subject of infertility and by an obstetrician or gynecologist from the United States on any topic selected by him. This would mean that an invitation to an American participant would be possible every fourth year and the honorarium would amount to about seventy pounds or the equivalent of some three hundred dollars.

The Royal College of Obstetricians and Gynecologists was founded in 1929 by W. Blair-Bell of Liverpool who was its first president with William Fletcher Shaw of Manchester as secretary. The latter, after having served as president for the past five years and being knighted, is now retiring from office and is being succeeded by Eardley Holland of London. The endowed lectureship commemorates Sir William Shaw's presidency and the anonymous donor wishes to demonstrate and further the friendship felt by our English colleagues toward the American profession. As such, it is worthy of our gratitude and appreciation. The postwar period with means of communication fully restored should witness the development of closer bonds between the great English-speaking countries. The interchange of ideas through the medium of personal contacts between groups interested in special branches of medicine can accomplish much, not only among the participants, but those whom they serve in a professional capacity. It is to be hoped that these objects may be possible of execution at an early date when the specter of war has been eliminated and opportunity offered again for more peaceful pursuits.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Cesarean Section

Marin, J. de Jesus: A Probable Solution of the Eternal Problem of Uterine Suture in Classical Cesarean Operation, *Rev. de cir. México* 14: 239, 1942.

J. de Jesus Marin has had 100 per cent satisfactory results in a series of fifty cases of classical cesarean section. The cases were entirely unselected and included those with ruptured bag of waters; patients in active labor; patients who had been examined several times; febrile cases; women with vertex, breech and shoulder presentations; and patients with previous cesarean sections. He ascribes the good results to the following factors: scrupulous preoperative preparation; thorough vaginal and peritoneal hygiene; protection of the abdominal cavity with pads of absorbent material, and strict adherence to his modified technique of uterine suture.

The author's method of uterine suture is as follows: The first row of sutures consists of heavy silk sutures inserted in the upper wound commissure, in the middle, and in the region of the lower commissure; between these sutures are inserted chromicized catgut No. 3 sutures spaced 2 cm. apart. These sutures take in all of the uterine wall with exclusion of the mucosa and the serosa. After all the sutures have been inserted the knots are tied firmly. The surface of this first row of sutures is then thoroughly disinfected. A continued chromicized catgut No. 2 suture is then anchored  $\frac{1}{2}$  cm. above the upper wound commissure. If the bag of waters had ruptured several hours before operation, and to prevent alarming postoperative distention, a warmed ampoule of 50 to 200 c.c. of amfetin (Lilly) is then poured into the abdominal cavity. Before closing the abdomen completely, a wick of braided silk is left for drainage of the cellular tissues, which is removed after 48 hours.

J. P. GREENHILL.

Perez, Manuel Luis, and Echevarria, Ramon: Prophylactic Intraperitoneal Sulfanilamide Therapy in Obstetric Surgery of Infected Cases, *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 234, 1942.

Perez and Echevarria report the results in 11 patients. Their procedure was as follows: After opening the abdomen and performing cesarean section, sulfanilamide was distributed in the following areas: the uterine cavity, the cervico-segmental wound, the isthmus, and the suture line of the visceral peritoneum. Half or two-thirds of the drug was placed in the lower abdominal peritoneum, and finally some sulfanilamide was left in the subcutaneous cellular tissues. The dosage used was 4 Gm., except in frankly contaminated cases, where it was increased to 6 and 8 Gm. However, the latter dose proved excessive, for unfortunately, one patient died of sulfanilamide intoxication as shown by the findings on necropsy.

Although the results in such a small series are not conclusive, they were very gratifying, considering that all cases were suspected of infection or were frankly infected. In no case did peritonitis or any other significant septic process develop. There was only one case of subcutaneous cellular phlegmon and two of hematoma, one in the subcutaneous tissue, and the other in the broad ligament.

Owing to large doses of the drug in some cases there was elevated temperature, cyanosis of the face and extremities, and slight reduction in the red cell count and percentage of hemoglobin, for a few days. There were, however, no renal complications, and in one case the drug was used despite the presence of hypertension and 1.5 per cent albumin in the urine.

J. P. GREENHILL.

Kletzhändler, M.: Uterine Rupture After Cesarean Section, *Monatsch. f. Geburtsh. u. Gynäk.* 113: 305, 1942.

In the Zurich Clinic from 1920 to 1938, there were 812 cesarean sections. During this time three uteri ruptured following cesarean sections performed in this clinic, and three additional cases of rupture of the uterine scar from operations performed elsewhere were also encountered.

The author reviewed 268 articles dealing with 402 cases of rupture of the uterus. In this review of the literature there were 141 ruptures of the scar following classical operations, 55 after the transverse fundal incision, 87 after the cervical longitudinal incision, 5 after the cervical transverse incision and in 104 cases information was not given.

About four-fifths of all the mothers were saved by operation and about the same proportion of babies died as a result of uterine ruptures. The same results were obtained with hysterectomy as with suture of the laceration.

J. P. GREENHILL.

Ribeiro, Eurico Branco: Intramural Pituitrin in Cesarean Operation, *Bol. do Sanat. Sao Lucas* 3: 179, 1942.

Eurico Branco Ribeiro (Sanatorium Sao Lucas) had used intramural pituitrin for ten years with very satisfactory results. Contraction of the uterus follows immediately, separation of the placenta is facilitated, hemorrhage is greatly reduced, the operative field is cleansed, the visibility of the edges of the uterine incision is enhanced and suturing can be carried out with more precision and security; all these facts lead to a more speedy conclusion of the operation. The technique is simple. Before the operation the contents of two ampoules of pituitrin are drawn into a syringe and the injection held ready. Immediately after extraction of the fetus, the pituitrin is injected into the anterior wall of the uterus.

J. P. GREENHILL.

Bazul, Victor Manuel: Contribution to the Study of Segmental Cesarean Operation, Thesis for M.D. degree, Peru 1: 189, 1941.

Victor Manuel Bazul discusses the history and indications of cesarean section and stresses the importance of the cervical method. He describes the extraperitoneal and transperitoneal methods, with their indications, disadvantages and complications, and cites a number of cases in which these methods were used. Cervical cesarean section is safest for mother and fetus. The method may be used in clean, suspected and infected cases without jeopardizing the general condition of the woman or exposing her to peritonitis. It allows the use of trial labor and avoids embryotomy of the living fetus. It permits the development of subsequent pregnancies without fear of uterine rupture. The extraperitoneal method is preferred despite the complexity of its technique, because of its excellent results: 13 cases gave no maternal mortality and a fetal mortality of 7.05 per cent. The transperitoneal method is the best for the practitioner because

of its simplicity: with the technique of Opitz, twenty-five cases gave a maternal and fetal mortality of 4 and 8 per cent respectively. Cervical cesarean section is now used in all the maternities of the world, and its diffusion in Peru will contribute to decrease the mortality rate of cesarean section.

J. P. GREENHILL.

**Gonzalez, Juan B., and Cutuli: The Infected Case. Its Symptomatology and Significance as Basis for the Indication of Cesarean Section in the Presence of the Risks of Symphysiotomy, Bol. Soc. de Obst. y Ginec. de Buenos Aires 21: 157, 1942.**

Juan B. Gonzalez and Cutuli call attention to the reduction in the percentage of cesarean section for contracted pelvis in the native statistics which they studied. These statistics include 198 cases of symphysiotomy for contracted pelvis, with five deaths (2.52 per cent) 139, (70.20 per cent) were impure cases with one death (0.71 per cent) due to peritonitis. The 116 impure cases treated by laparotomy gave a maternal mortality of 13.82 per cent and a peritoneal infection rate of 6.03 per cent; in 56 of these cases, the indication for laparotomy was disproportion between the pelvis and fetal head: the maternal mortality was 10.71 per cent and the peritoneal infection rate, 7.14 per cent. This shows the superiority of symphysiotomy over all modern methods of cesarean section in the treatment of relative bony dystocia. These comparative figures should be of special interest to foreign schools which admit that cephalopelvic disproportion constitutes from 55 to 75 per cent of their indications for cesarean section.

J. P. GREENHILL.

**Leon, J.: Artificial Extraperitoneal Cesarean Section. Author's technique, Arch. Clin. obst. y ginec. 1: 402, 1942.**

Leon adds twenty-one more cases of his own extraperitoneal cesarean section to the twenty already reported. The uncorrected maternal mortality was 10.2 per cent which is satisfactory considering that many of the patients were frankly infected. The fetal death rate was 7.3 per cent.

J. P. GREENHILL.

**Thomas, Rufus C.: Cesarean Section Under Spinal Analgesia, J. Obst. & Gynaec. Brit. Emp. 49: 3, p. 247, 1942.**

The author mentions that the ideal anesthetic in cesarean section is the one which carries the highest degree of safety to mother and child and is also the one which offers the maximum operative comfort to the surgeon. The child is unaffected by the anesthetic and any marked degree of asphyxia is rare. The operation is made easier for the surgeon because of the marked relaxation. Spinal anesthesia does not interfere with satisfactory uterine contractions. The author reviews the literature on the subject and quotes the various arguments for and against spinal anesthesia in cesarean section.

In his own cases (121) Thomas used perraine (Ciba). Atropine gr.  $\frac{1}{100}$  and ephedrine gr.  $\frac{3}{4}$  were given preoperatively. Where the patient had a test of labor under twilight, section was not carried out under two hours after the last medication. Mental tranquility of the patient is of utmost importance. In cases of placenta previa, the patient should be held by an attendant for the injection to prevent any increase in intra-abdominal pressure which might cause bleeding.

Two patients developed headaches which after spinal anesthesia persisted for several days. Three developed chest complications; four thrombophlebitis. Post-

operative distention was rare and there were no cases of secondary hemorrhage. Five patients had 2 sections under spinal anesthesia. One death occurred on the ninth postoperative day from pulmonary embolism.

WILLIAM BERMAN.

### Obstetric Operation—Cesarean

Pla, P., and Ricci, G.: Spinal Anesthesia in Cesarean Section, *Bol. soc. de obst. y ginec. de Buenos Aires* 20: 817, 1941.

The authors state that patients are now carefully selected to insure maximal safety in spinal anesthesia: those with disease of the nervous system, syphilis, pernicious anemia, marked hypertension or hypotension, labile circulation, shock and hemorrhagic conditions are excluded. Patients, who have lost blood but have a normal blood pressure and no signs of shock, must be added to this list. The technical conditions to be observed are premedication with ephedrine, morphine and atropine, sitting position, low puncture, smallest possible amount of anesthetic, allowance of necessary time for fixation of the anesthetic and only then decubitus and careful change to Trendelenburg position if indicated; twenty minutes later, another injection of ephedrine to prevent the fall of blood pressure so characteristic of this anesthesia. Nevertheless, some unpredictable accidents still occur.

From 1934 to 1941, the authors used spinal anesthesia in 45 cesarean sections. Among 36 cases, the anesthetic was tutocain in 23, novocain in 9, percain in 3 and metocain in one. Therefore, there were six serious accidents with three deaths by bulbar syncope: one each with tutocain, novocain and metocain anesthesia. This is a high mortality, which becomes even more significant by comparison with the number of daily operations for gynecologic disorders in which the same anesthetic technique is used without fatality. The accidents suggest the possibility of a special susceptibility of the pregnant woman for spinal anesthesia and particularly for novocain or other compound of this type. The accidents were characterized by rapid diffusion of the anesthetic, cyanosis, arrest of breathing thread-like pulse, hypotension and syncope. The symptoms did not respond to oxygen-carbon, ephedrine, coramine or other emergency medication. One patient died during the operation and the other two lingered on for four days without recovering from the hypotensive adynamic condition caused by the anesthetic.

The authors restrict spinal anesthesia to ideal cases of obstetric surgery and prefer the use of tutocain which, in 0.03 to 0.05 Gm. doses, gives optimal results.

J. P. GREENHILL.

### Endocrinology

Kern, E. S.: Prothrombin in Mother and Child: Investigation of the Prothrombin Content of the Mother's Blood in Pregnancy, Labor and the Puerperium as Well as in the Newborn; the Role of Vitamin K in Obstetrics, *Monatschr. f. Geburtsh. u. Gynäk.* 114: 47, 1942.

The author's investigations showed that the prothrombin content of the blood of normal women in the first few months of pregnancy varies from 103 to 113 per cent. From the fifth month until the end of pregnancy the prothrombin content rises and attains a maximum of 134 per cent in the tenth month. During labor it falls to 116 per cent and rises again during the puerperium without, however, reaching the high point of 134 per cent.

The prothrombin content of the newborn is about 60 per cent. There is no direct relationship between the maternal and the infant prothrombin content.

The variations in the maternal prothrombin content during pregnancy and the diminished prothrombin content in the infant, are probably due more to endogenous factors than to variations in the intake of vitamin K.

J. P. GREENHILL.

Jones, G. E. Seegar, and TeLinde, R. W.: *An Evaluation of Progesterone Therapy in the Treatment of Endometrial Hyperplasia*, Bull. of the Johns Hopkins Hosp. 71: 5, 282, 1942.

The authors have considered the following facts for the successful use of progesterone in the treatment of endometrial hyperplasia:

1. Progesterone as substitution therapy and associated endocrine abnormalities which may be contributing factors in the disease must be investigated.

2. The dosage and time interval of administration must be adequate.

3. Progesterone is not useful in checking immediate hemorrhage. It is used for preventive purposes and must generally be continued cyclically over a period of at least four months.

4. A recurrence of the disorder will not be prevented by progesterone. Hormone studies performed on a selected group of cases showed no pregnandiol in the urine before treatment, and no excessive urinary gonadotropin. Estrogen values were within the normal range.

C. O. MALAND.

Heckel, George P.: *The Estrogen Sparing Effect of Hysterectomy*, Surg., Gynec. & Obst. 75: 379, 1942.

The author was able to demonstrate that corpora lutea of pseudopregnancy in the rabbit may be prolonged by the removal of the uterus. Furthermore, an amount of estrogen insufficient to prolong the corpus luteum will achieve this effect if a sufficient amount of the uterus has been removed. Based on the supposition that the uterus uses this substance, the author hypothesizes that hysterectomy produces an estrogen sparing effect.

L. M. HELLMAN.

Brewer, John I., Jones, Harold O., and Skiles, J. H.: *Effect of Gonadotropic Substance on Ovulation*, J. A. M. A. 118: 278, 1942.

The authors report their experiences in the use of pregnant mare serum. The injections were given intramuscularly throughout the entire course. The patients treated were all to be operated upon later. Half of the group were operated upon in the first half of their menstrual cycle. The second group was operated upon in the second half of the cycle. An untreated group of patients was used as control. In the treated group of twenty-four patients, thirteen possessed corpora lutea of the current cycle. A microscopic study of eleven of these thirteen patients indicates definitely that ovulation could not have occurred as a result of the intramuscular injection of the gonadotropic substance. In the control group of twenty-two patients, sixteen patients possessed corpora lutea of the present cycle. There was no demonstrable increase in ovulation in the treated group. Ovulation was not induced in the treated patients either early or late in the cycle. The simultaneous induction of ovulation of more than one follicle was not brought about as a result of the therapy. An attempt failed to induce ovulation before or after spontaneous ovulation.

WILLIAM BERMAN.



## Gynecology

Arenas, N., and Roganti, A.: Unusual Evolution of Pyosalpinx, *An. del Inst. de mat. y Asis. Soc. (Buenos Aires)* 3: 1941.

A thorough discussion of pyosalpinx accompanies the report of the authors' interesting case of a young woman who was hospitalized shortly after marriage with bilateral pyosalpinx. One of the abscesses spontaneously opened into the rectum. Abdominal palpation revealed a large mass in the right iliac fossa. Expectant treatment was followed for approximately two months while the mass increased in size. At length, a 4 cm. incision was made over the most central and fluctuating part of the abscess, with abundant drainage and subsequent recovery of the patient.

ROBERT J. WEISSMAN.

Brines, Osborne A., and Blain, James H.: Adenomyosis of the Uterus, *Surg. Gynec. & Obst.* 76: 197, 1943.

The authors report a ten years' study of adenomyosis during which period 73 cases were observed. This represented an incidence of 10.7 per cent of all the uteri removed. A brief review of the literature is given and the confusion in the existing terminology pointed out. The authors emphasize that, strictly, adenomyosis is defined as the occurrence of heterotropic endometrium within the myometrium, unassociated with tumor formation. There may or may not be a general hyperplasia of the myometrium, and there generally is a slight nodularity of this layer. It is stated that this condition is thus differentiated from adenomyoma on one hand, and endometriosis on the other. The location of the islands of endometrial tissue, more frequently on the inner half of the uterine wall would suggest invasion as the mechanism of production, however, by means of special stains and a consideration of the embryogenesis, the authors reach the conclusion that the aberrant endometrial islands are derived from dedifferentiated myometrial cells capable of forming endometrial stroma or glands. Adenomyosis can definitely be said to be benign.

L. M. HELLMAN.

Black, Elinor F. E.: The Use of Testosterone Propionate in Gynecology, *Canad. M. A. J.* 47: 124, 1942.

Case reports are cited to illustrate the use of testosterone propionate in gynecology. The indications given are menorrhagia, glandular hyperplasia of the endometrium, menopausal bleeding due to glandular hyperplasia of the endometrium and small uterine fibroids, mastalgia, and inhibition of lactation. In the presence of a fibroid in a young man, testosterone propionate failed to control bleeding.

The author emphasizes that cases must be carefully chosen and that such conditions as retained products of conception, uterine and cervical polyps and malignancies must be ruled out. Preliminary curettage is often necessary. The tendency to masculinization must not be minimized even though this effect is transient.

CARL P. HUBER.

## Endometriosis

Salaber, Juan A., and Nogues, Armando E.: Uterine Isthmic Endometriosis Perforating Into the Parametrium, *Bol. soc. de obst. y ginec. de Buenos Aires* 20: 770, 1941.

The authors state that the incidence of endometriosis of the genital system is increasing, but that endometriosis of the parametrium is relatively rare. It may be primary or secondary. Clinically, endometriosis of the broad ligament occurs

as a slightly movable or fixed tumor, a more or less diffuse infiltration of the cellular tissue of the parametrium which acquires a hard, ligneous consistency. It is sensitive to pressure and its symptoms become more marked during menstruation. Painful dysmenorrhea is the constant and outstanding symptom of this form of endometriosis and presents the clinical characters described by Hunner in strictures of the pelvic ureter due to compression by infiltrating pathologic processes of the parametrial tissues. In localization and irradiation, the pain resembles the colic of a passing calculus, but it varies in intensity and extension; it is usually described as severe, diffuse, local and lateral; it may begin one week before menstruation and persist with varying severity until menses are established, or it may coincide exactly with menstruation. The clinical character of the dysmenorrhea and the disappearance of the latter with the elimination of the ureteral stricture suggest that the pain is due to premenstrual congestion which increases the ureteral stenosis and the volume of the tumor tissue. This interpretation is supported by the authors' case in which the pain was relieved after menstruation and exacerbated at the following menstruation before operation. Treatment must be radical because of the impossibility of extirpating all the involved tissue. An important point is ample liberation of the ureter from all compressing tissues to eliminate the dilatation of the ureter and renal pelvis.

J. P. GREENHILL.

Jessing, A.: Perineal Endometriosis After Prolapse Operation, *Acta. obstet. et gynec. Scandinav.* 112: 225, 1941.

Jessing reports a case of perineal endometriosis which occurred after a prolapse operation. It is assumed that the lesion arose from implantation during the operation because the uterus was curetted immediately before the prolapse operation.

J. P. GREENHILL.

Stephenson, R. T., and Graffagnino, P.: Endometriosis: A Problem of Treatment, *South. M. J.* 35: 525, 1942.

A survey of the files of the Charity Hospital of New Orleans for a four-year period during which there were approximately 24,000 admissions, revealed only forty-two cases of endometriosis. This is a very small number for so large an institution. The racial incidence of eighteen colored patients and twenty-four white patients is disproportionate to the Negro-white ratio of gynecologic admissions.

Seven patients were unmarried; of the remaining, seventeen were sterile and eighteen were parous. The age incidence varied between 20 and 55 years, the greatest number occurring in the later functional years. Endometriosis was the primary pathologic condition in twenty patients, while in twenty-two there were other associated conditions. Fourteen patients, thirteen of whom were colored, also had "fibroids." Three patients, all colored, had chronic pelvic inflammatory disease.

Pain, which is the symptom most frequently encountered, occurred in twenty-five cases; in thirteen of these, endometriosis was the principal pelvic condition. It was not related to menstruation in fifteen instances, while in the others, the time relation was variable. The most frequent pelvic physical findings, which occurred either alone or in combination, were, uterine displacement, fixation, prolapse, and adnexal masses. Except for a single case in which involvement of the sigmoid colon occurred, the distribution of ectopic endometrium was limited to the pelvic organs; in three patients it was generalized in the pelvis.

The diagnosis may be easy or difficult. Where the characteristic nodules may be palpated in the vaginal wall, it is fairly obvious. The condition should be suspected when dense pelvic adhesions are encountered in the absence of typical

history and other findings of pelvic inflammatory disease. Under the same circumstances the diagnosis is strongly suggested by a complaint of acquired dysmenorrhea which becomes progressively worse. In five of the twenty primary cases of endometriosis, the diagnosis was made at operation, and, in the other five cases, histopathologic confirmation was required.

The only certain method of cure is removal of ovarian tissue. Treatment must be individualized. Factors to be considered when therapy is planned are, the age and economic status of the patient, the degree of the pathologic process, and the desire for children. In the older patients there is less indication for conservatism. Radical operation was performed in the twenty-two patients in whom there was associated pelvic disease, the latter condition, of itself, constituting an indication for the procedure. Of the twenty patients whose primary pelvic condition was endometriosis, fifteen were treated by radical surgery; conservative procedures consisting of partial oophorectomy and cauterization of endometrial transplants were employed in four patients. One patient refused any surgical treatment and was referred to clinic.

ARNOLD GOLDBERGER.

### Extrauterine Pregnancy

Olivier, Claude: Cullen's Sign, *Presse méd.* 48: 593, 1940.

The author describes an obscure case of an ectopic pregnancy resulting in tubal abortion with minimal intra-abdominal bleeding. The only positive clinical finding other than a small palpable juxtauterine mass was a positive Cullen Sign.

The writer reviews the literature on the history and significance of circumnavel cutaneous discolorations. He credits Hofstatter, who reported such a condition in 1909 following surgery, as the first to report such a sign but admits that Cullen was the first to utilize the sign as a preoperative indication of hemoperitoneum.

The author concludes that Cullen's Sign is of rare but nonetheless significant value as a supplemental aid to diagnosis in atypical cases of hemoperitoneum.

CLAIR E. FOLSOME.

### Menopause

Gessler, G.: The Influence of Folliculin Injections Upon the Glycemia of Postmenopausal Diabetic Women, *Presse méd.* 48: 780, 1940.

Large doses of estradiol benzoate were given, hypodermically, to four postmenopausal diabetic women. In two cases where the diabetes appeared first during the advent of the menopause, the follicular hormone provoked an early decrease in their glycemia. This decrease in the glycemia persisted only several days following the last hormone treatment. In two other cases, where the diabetes and menopause did not occur simultaneously, the decrease of glycemia with use of estradiol benzoate was not as constant.

The author explains the different responses to treatment by reasoning that in the former two cases the diabetes was, in part, of hypophyseal origin: that the hypersecretion of the gonadotropic hormone induces in these cases an "exaggerated diabetogenic factor"; and that injections of the follicular hormone inhibit the gonadotropic hormone to thus lower indirectly the glycemic level. In the latter two cases, where the diabetes and menopause did not occur at the same time, the anterior pituitary did not contribute to the etiology of the patients' diabetic conditions. The author notes that it requires at least 5 mg. of estradiol

benzoate to produce a lowering of the glycemia. He concludes that basal metabolism is little affected by the use of estradiol benzoate.

CLAIR E. FOLSOME.

### Physiology of Pregnancy

Tapernoux, F.: The Qualitative Relationships of the Aschheim-Zondek Reaction at the End of Pregnancy and in the Puerperium, *Monatsschr. f. Geburtsh. u. Gynäk.* 113: 233, 1942.

The author found that in the presence of intrauterine fetal death, there are great differences in the excretion of the gonadotropic hormone. Occasionally Reaction I of the Aschheim-Zondek test remains positive for many months after fetal death. In four cases, Aschheim-Zondek tests were performed at the end of pregnancy and in the puerperium, and the genitalia of the mice used for the biologic tests were studied microscopically. The author found that there was an early disappearance of Reactions II and III. He emphasizes that quantitative factors of the test are important.

J. P. GREENHILL.

Del Castillo, E. B., and Pasqualini, R. Q.: Diabetes Insipidus During Pregnancy and After Castration, *Médecina, México* 2: 335, 1942.

The authors describe two cases. The first woman had two normal pregnancies which did not change the diuresis, or influence the amount of posterior hypophyseal lobe powder required to maintain the diuresis within normal limits. The second woman had diabetes insipidus since she was 18 and underwent a bilateral ovariectomy at the age of 36, which had no effect on the polyuria; 150,000 international units of estradiol benzoate given in one week were also without effect. Accordingly, diabetes insipidus is independent of pregnancy and castration and is uninfluenced by the estrogens. Nasal aspiration of powder of posterior hypophyseal lobe produced a satisfactory reduction of the diuresis in both cases. Finally, implantation of bovine posterior lobe in the first case produced an anti-diuretic action lasting three months, and an injection of five vasopressor units of pitressin tannate in oil in the second case, had an antidiuretic effect for about 48 hours, while 10 units acted satisfactorily for seven days.

J. P. GREENHILL.

### Diagnosis of Pregnancy

Goldman, Lester M., Kessler, Henry B., and Wilder, Mildred E.: The Colostrum Cutaneous Test for the Diagnosis of Pregnancy, *J. A. M. A.* 119: 130, 1942.

A group of 185 tests on antepartum cases were analyzed. One hundred and thirty-one, or 70.8 per cent, showed a negative reaction indicative of pregnancy, while fifty-four, or 29.2 per cent, showed a positive reaction. The period of gestation in those giving a correct response ranged from 9 to 39 weeks. In the post-partum group of 30 tests, there were 17 correct reactions or 56.6 per cent and 13 incorrect or 43.4 per cent.

In the control group the total number of cases performed was 153. The total number of correct reactions among this group was 103 or 67.3 per cent. This latter group included 40 men.

All together the authors' series showed about 70 per cent of all pregnancies had no sensitivity, while about 70 per cent of all nonpregnancies showed a reaction of sensitivity. It is therefore felt that in the authors' hands the colostrum cutaneous test does not appear to offer a valuable diagnostic procedure for pregnancy.

WILLIAM BEEMAN.

Verhage, J. C.: *The Significance of Ketonemia and Ketonuria in Pregnancy*, *Monatschr. f. Geburtsh. u. Gynäk.* 113: 1, 1942.

No rise in the amount of ketone bodies of the blood was found in pregnancy. When ketonemia is found during pregnancy or labor especially when it occurs in women with hyperemesis, it is the result of insufficient food intake. The rise in the amount of ketone bodies in the blood and urine as a result of starvation varies considerably in pregnant women. Ketonemia and ketonuria quickly disappear after sufficient intake of food.

J. P. GREENHILL.

Balbi, J.: *The Question of Clinical and Roentgenologic Evaluation of Overterm Pregnancy*, *Monatschr. f. Geburtsh. u. Gynäk.* 113: 121, 1942.

The author attempted to discover signs which would reveal definite post-maturity. He came to the conclusion that there was only one way of deciding that a normal period of pregnancy had been passed. The criterion is the size of the abdomen. If the abdomen does not increase in size, or if it decreases after the calculated date, we may assume that pregnancy is going beyond term. The size of the child cannot be used as a criterion. Likewise, roentgenologically, the ossification centers of the bones cannot be used to judge the duration of pregnancy.

J. P. GREENHILL.

Fontava, G.: *The Mineral Composition of the Bones in Pregnancy*, *Monatschr. f. Geburtsh. u. Gynäk.* 113: 57, 1942.

Investigation of the mineral composition of the femurs of pregnant guinea pigs showed that there is very little change in the calcium phosphate content during various stages of pregnancy. The number of young play no role. The author maintains that the minerals necessary for the development of the fetal skeleton under physiologic conditions are derived from the nourishment from the mother. The maternal bone reserves are not tapped.

J. P. GREENHILL.

## Placenta

Biekers, William: "The Placenta: A Modified Arteriovenous Fistula," *South. M. J.* 35: 593, 1942.

Burwell first suggested that most of the circulatory alterations occurring during pregnancy could be explained by assuming the placenta to be a modified arteriovenous fistula. The author repeated his work on the femoral venous pressures in pregnancy and made some original observations which confirm Burwell's thesis. The anatomic and physiologic basis for this concept is briefly outlined.

In a series of twenty-three primigravid patients, the femoral venous pressures and arm pressure were measured in the last weeks of pregnancy, the determinations being made on the same day. The results were correlated with the presence of lower extremity edema, which was measured with a centimeter tape, and with the site of placental attachment as determined by intrauterine palpation at the completion of the second stage of labor. Labor started spontaneously in all the patients, and, with the single exception of cesarean section performed for central placenta previa, delivery was accomplished by outlet forceps.

Whereas, in nonpregnant women, venous pressures in the arms and legs are approximately the same, in pregnancy the venous pressure of the lower extremities averages 100 to 150 mm. higher than that of the arm. This cannot be ex-

plained by the mechanical effect of the enlarged uterus. When the swelling of the ankles was unequal, it was noted that the edema was greatest on the side where the placental bruit was most distinct, and, that the femoral venous pressure was greatest on the same side.

Eight patients had clinical edema and the average femoral venous pressure exceeded that in the arm by 120 mm. ( $H_2O$ ); in the nonedematous group, the average difference was 100 mm. The most frequent placental sites are, first, the posterior uterine wall; next, the lateral walls. In the twelve instances in which the placenta was implanted either anteriorly or posteriorly, the femoral venous pressures were approximately equal, as was ankle edema. The remaining two placentas were attached laterally, and the femoral venous pressure on the corresponding side averaged 28 mm. higher than that on the opposite side. The greatest venous pressure difference upper and lower extremity occurred in the patient with placenta previa; here the highest femoral venous pressure was recorded (260 mm.). The action of the placenta as an arteriovenous fistula is the only explanation for these observations.

ARNOLD GOLDBERGER.

### Sterility, Fertility, Contraceptives

Dorn, Harold F.: The Potential Rate of Increase of the Population of the United States, *Am. J. Soc.* 48: 173, Sept., 1942.

Dorn, of the U.S.P.H.S., states, after a review of late government statistics at the National Health Institute, it can be demonstrated that the fertility and mortality of the population of the United States, during the eleven-year period ending with 1941, was at least sufficient to maintain a stationary and possibly a slowly increasing population.

It is estimated now that probably 93 to 94 per cent of the white births and from 80 to 87 per cent of the colored births are registered. Dorn predicts that it may be stated, with considerable confidence, that the birth rate in 1943 and perhaps that for 1942 will be lower than the rate in 1941. (*U. S. Division of Vital Statistics provisional figure for the first 6 months of 1942 was 19.7 per 1,000.*)

Marriage and birth rates decreased rapidly after the 1929 depression, but the deficit in marriages was wiped out by the end of 1940. The average annual number of marriages (1921 to 1930) was 1,185,000 which increased to 1,284,000 (1931 to 1940). By the end of 1941, there will likely be an "excess" instead of a deficit in marriages.

The Selective Service Act's enactment in September, 1940, and the declaration of war in December, 1941, increased the number of marriages which would, in ordinary times, have been postponed for several months or even years. The increase in marriages in 1941, however, was most likely resultant from increased industrial activity. As would be expected, the increase in the birth rate (7.8 per cent higher for the first 4 months of 1942, compared to the corresponding 4 months of 1941) increased following enactment of the Selective Service Act. Our greatest decline in birth rate will not come probably until large expeditionary forces are sent overseas.

The reproduction for the white population (1930 to 1941) was approximately 100, while that for the nonwhite population was definitely above the replacement level. The increase in the crude birth rate, since 1933, has resulted almost entirely from an increase in the number of the first and second births and does not represent an increase in the lifetime fertility of women in the childbearing ages.

CLAIR E. FOLSONE.

**Pineda, Rafael:** *Kymographic Insufflation in Female Sterility*, An. brasil. de ginec. 13: 265, 1942.

Pineda describes the Rubin apparatus and technique, and lists the indications, contraindications and dangers of the method as stated by Rubin. He has used the insufflation technique in one hundred patients during the past six months. To date, five pregnancies occurred in cases with primary sterility (in one of which it extended over 17 years and in two over five years), and two pregnancies in secondary sterility.

J. P. GREENHILL.

**Lastra, Enrique Thwaites, and Jakob, Alfredo:** *Results of Surgical Treatment of Sterility*, Bol. soc. de obst. y ginec. de Buenos Aires 21: 327-331, 1942.

Enrique Thwaites Lastra and Alfredo Jakob report that following plastic operations on the tubes four of ten patients became pregnant. Three had full-term pregnancies and one had an ectopic pregnancy. The authors think the reason for their success lies in the fact that they operated only on clean cases, i.e., the patients had more or less healthy ovaries, they had no adhesions and the sterility was due to occlusion of the tubes in the isthmic region while the fimbriae were normal. The technique consisted of extirpation of the occluded portion and re-implantation of the tube as far as the uterine cavity. All patients with occlusion in the isthmic region are advised to submit to the operation if they desire to have children, but success is not guaranteed. Postoperative care is important; hystero-graphy must be performed.

J. P. GREENHILL.

**Jaffe, A. J.:** *Urbanization and Fertility*, Am. J. Soc. 48: 48, 1942.

In an extensive study of the relationship of urban to rural fertility, in which the rural fertility for a given area was given an index of 100, comparative urban areas had fertility indices as low as 50. The author is not inclined to give too much weight to contraceptive practice as a factor in reducing urban fertility. Abortion, sexual difficulties, legal restrictions and postponement of marriage as well as the practice of infanticide in some areas, all apply to affect the fertility rate. The potential number of children the average woman can bear is well in excess of 6 or 7, and it is evident that some form of birth control is practiced even in remote areas having available statistics where modern contraceptive techniques were not available. Fertility rate falls with increased desire for a better standard of living in any given group.

R. J. WEISSMAN.

**Guttmacher, A. F.:** *The Contraceptive Clinic and Preventive Medicine*, Human Fertil. 7: 1, 1942.

The author feels it is the function of the contraceptive clinic to implement the more positive medical contraindications to pregnancy such as are found in women having heart disease, diabetes, tuberculosis, etc., as well as in psychotics and epileptics. The fact that the indigent and mentally defective are invidiously exceeding in reproduction those of normal mentality is not generally appreciated. Careful pelvic examination in the clinics is a new source of material for early diagnosis of malignancy as well as other conditions requiring medical or surgical attention. Finally, says the author, there is no reason why treatment of sterility should not be an equally important function of these clinics.

R. J. WEISSMAN.

## Vaginal Infections

Woodruff, J. D., and TeLinde, R. W.: The Treatment of Gonococcal Vaginitis in Children With Diethylstilbestrol, *South. M. J.* 35: 389, 1942.

Because of the fact that most cases of gonococcal vaginitis are treated in free clinics, and, that the cost of estrogenic hormone derived from natural sources and so successfully employed in treatment, is high, the authors resorted to the use of the synthetic hormone diethylstilbestrol.

Fifty consecutive patients, forty colored and ten white, were treated orally or by vaginal suppositories, and the results compared. The routine of treatment required weekly observation with smears stained by the gram method. This was continued until 3 consecutive negative smears were obtained. Cultures were made before, during, and after treatment, and weekly saline vaginal washings were examined for the relative number of pus and epithelial cells. Following the termination of therapy results were checked at two and at six weeks' period, and subsequently at four to twelve months.

While the percentage of negative smears at the end of two weeks of treatment was about the same for both modes of administration of the hormone, the results were more uniformly successful and generally obtained with greater rapidity when suppositories were employed. For the latter, a dose of 0.1 mg. is recommended. The optimum oral dose was 1 mg. per day. Toxic symptoms occurred when 1 mg. was given three times daily, while 0.1 mg. per day, was inadequate.

Whereas, breast enlargement occurred in approximately 46 per cent of the suppository group of cases, and regressed in from four to six weeks, it developed in 94 per cent of the oral series, and in two instances required about four months to disappear. Other side effects occurred only in the latter group and included, uterine enlargement, the development of pubic and axillary hair, enlargement of the clitoris and vaginal bleeding. No evidence of "vaginal fixation" was noted, and the authors were of the opinion that the insertion of a suppository by the child's mother or nurse was less disturbing than the taking of smears by the physician. They are emphatically in favor of the suppository method and prefer it to oral administration for the reasons expressed.

ARNOLD GOLDBERGER.

Russ, J. D., G. Collins, Conrad, F.A.C.S., and Powell, Sam: Prepuberal Vulvovaginitis, *Clinics* 1: 117, 1942.

Prepuberal vulvovaginitis is discussed from the standpoint of physiology, pathology, diagnosis, criteria of cure, mode of transmission, and therapy. The introduction of estrogenic therapy represented a decided improvement over the use of antiseptics in the form of instillations, ointments, and douches. The authors have been impressed favorably with their results from the oral use of the synthetic estrogen, stilbestrol. They recommend 1 mg. crushed in milk given three times a day, orally. By the end of the fifth to seventh day of medication, vaginal smears show the absence of pus cells, absence of gonorrheal organisms, and the presence of a cornified adult type of vaginal epithelium. Biopsy of the infant vagina shows that this adult cornification remains about three or four weeks after discontinuation of the therapy. During the course of therapy, slight enlargement of the nipples and labia occurred, but these changes returned to normal and no untoward reactions were noted.

Apparently the oral administration of stilbestrol brings about the same local changes in the vagina which occur from the use of estrogens given in the form of vaginal suppositories.

HOWARD C. MOLOY.



# Correspondence

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## Treatment of Deficient Spermatogenesis

*To the Editor:*

Although in agreement with most of the facts contained in the letter by Dr. Abner L. Weisman in the October, 1943, issue of the JOURNAL (page 618), I am not in accord with the following statement. Dr. Weisman states, "Can we stimulate spermatogenesis where it has faltered? It is almost universally agreed that in azoospermia, endocrines and the like, have failed miserably in the treatment of deficient spermatogenesis." Except in cases of double occlusion of the male genital tubes, I have never failed to bring about an improvement and in many cases a cure of deficient spermatogenesis by the use of the anterior lobe of pituitary gland extract in large doses and given by mouth for a period of six months or less. I prescribe 80 grains a day (16 five-grain tablets). The expense to the patient is very large but it is important to give it in these very large doses and to achieve a result.

MAX HUHNER, M.D.

88 CENTRAL PARK WEST

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## ANNOUNCEMENT

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### The Registry of Ovarian Tumors

About one year ago announcement was made of the fact that the American Gynecological Society had undertaken the sponsorship of an American Registry of Ovarian Tumors, and that it had appointed from its Fellows a committee of five gynecologic pathologists to carry on this work. Gynecologists and pathologists were urged to send material from unusual ovarian tumors to this Committee for study and classification, with the hope that an intensive and cumulative study of this sort would in time throw much needed light upon the pathology, clinical characteristics and perhaps even the histogenesis of some of the still poorly understood tumor types encountered in the ovary.

The response to this first announcement has been gratifying, but it is obvious that it escaped the notice of many readers of the JOURNAL, and that many of those who saw it have not realized the potential value of a concerted study of this sort. We are, therefore, making this second plea for the cooperation of clinicians and pathologists throughout the country. Heads of gynecological departments and pathological laboratories especially are asked to see to it that slides or tissue from all interesting and unusual ovarian tumors are sent to the Committee, together with an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, operative findings and procedures, together with a gross description of the tumor, and photographs, should these be available. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent formalin. Where only slides are available, these should be carefully packed in wooden or metal slide containers to avoid breakage in the mails.

It should again be emphasized that the function of the Committee is not to render a purely diagnostic service, and that quick reports as to its collective opinion are not possible because of the time consumed in passing the material between the members of the Committee, scattered as they are in various parts of the country. When the study of the material submitted is complete, the contributors will be notified as to the final classification of the tumors in the Registry.

Since there is still much uncertainty as to the prognosis of certain tumors of the ovary, it is hoped also that information can be accumulated as to the subsequent course of the patients, particularly those with tumors of malignant or doubtful nature. To facilitate such a follow-up study, those who send in material are asked to supply the name of the attending surgeon or family physician, so that subsequent information as to the clinical course may be obtainable.

The Registry is to be looked upon as a cooperative project among the gynecologists and pathologists of this country, and it is earnestly hoped that all will develop the routine of sending material from all interesting ovarian tumors, with the above indicated data, to the Committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore, Md.

EMIL NOVAK, CHAIRMAN  
ROBERT MEYER  
HERBERT F. TRAUT  
GEORGE H. GARDNER  
KARL H. MARTZLOFF

# Items

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## Progress of The E. M. I. C.

It may be of interest to note, as announced by the Federal Children's Bureau, that the total number of maternity and pediatric cases for which care has been authorized from the funds appropriated by Congress for this purpose through October 31, 1943, is 99,336. Five states, Connecticut, Colorado, Louisiana, North Dakota, and Texas, as well as the Territory of Puerto Rico, are not included in the program.

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## American Board of Obstetrics and Gynecology, Inc. Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944, at 2:00 P.M.

Arrangements will be made so far as is possible for candidates in Military Service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 12, 1944, Part I examination, who are entering Military Service, or who are now in Service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding the records to the Office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

The Part II examination will be held at Pittsburgh, Pennsylvania, from June 9 to 14, 1944. Notice of the exact time and place of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations applying to civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

November 16, 1943.

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 842 Park Ave., New York, N. Y. Annual meeting Chicago, May 15, 16, 17, 1944.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting not yet decided.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting cancelled.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting Chicago, May 8-12, 1944.
- New York Obstetrical Society.** (1863) *President*, W. T. Kennedy. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Catharine Macfarlane. *Secretary*, J. B. Montgomery, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, George H. Gardner. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, James P. McManus. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fair, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, David B. Ludwig. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

- New England Obstetrical and Gynecological Society.** (1929) *President*, Frank A. Pemberton. *Secretary*, Fred. J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, J. Keith Cromer, 1835 Eye St., N.W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, R. Glenn Craig. *Secretary*, D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Norman F. Miller. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Gerhard Ahnquist, 1336 Madison Street, Seattle. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Meehler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, Geo. D. Huff. *Secretary*, Frank Russell, 233 A St., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, John D. Graham, Devil's Lake. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Sehamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

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## Original Communications

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### ON THE DEVELOPMENT OF THE EARLY HUMAN OVUM, WITH SPECIAL REFERENCE TO THE TROPHOBLAST OF THE PREVILLOUS STAGE: A DESCRIPTION OF 7 NORMAL AND 5 PATHOLOGIC HUMAN OVA\*

ARTHUR T. HERTIG, M.D., AND JOHN ROCK, M.D., BOSTON, MASS.

*(From the Free Hospital for Women, Brookline, Mass., the Departments of Pathology, Obstetrics, and Gynecology, Harvard Medical School, and the Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.)*

THE purpose of this paper is to describe the early morphologic development of the normal human trophoblast and to compare it with corresponding phases in the development of abnormal ova. The observations recorded encompass a period beginning shortly after implantation of the blastocyte, on about the seventh day, and extending to about the fourteenth day when chorionic villi appear; this time interval coincides with the twenty-first to the twenty-eighth day of the normal menstrual cycle; that is, the week preceding the first missed period of the pregnancy. In addition, one villous embryo of 16.5† days is included for the sake of completeness.

\*Read at a meeting of the Chicago Gynecological Society, Chicago, Ill., December 18, 1942.

This study has been aided by grants from the Carnegie Corporation of New York, the William F. Milton Fund of Harvard University, and the Committee for Research in Problems of Sex, National Research Council.

†The ages of the ova are recorded as mean values on the basis of coital dates in the particular case and/or comparative embryologic development in the macaque; for example, the figure 16.5 indicates that this ovum is judged to be between 16 and 17 days old.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

In studying the early development of the human ovum, one is confronted by the complicating fact that, whereas many problems in embryology can be approached or even solved through comparative investigation of lower forms, the problem of early human placentation must be studied directly with human material. This is due to the scarcity of comparative material among subhuman forms, for in but one other primate family besides man, that of the anthropoid apes, has been discovered the so-called *interstitial* type of implantation<sup>1</sup> in which the blastocyst becomes completely embedded within the compact tissue of the endometrium. The only anthropoid specimen described in the literature which is comparable to the material considered in the present paper is the 10.5-day old chimpanzee ovum, "Yerkes A," reported by Elder, Hartman and Heuser.<sup>2</sup> Obviously, since in their study but one stage was described, information as to this type of implantation has been up to now incomplete. Indeed, the sole detailed description of placentation in any primate is the classic one of Wislocki and Streeter<sup>3</sup> on the monkey (*Macaca mulatta*). However, implantation in the macaque differs from that of man and the higher apes, since it is of the *superficial* type; i.e., the blastocyst embeds on the endometrium and thereby remains in the cavity of the uterus during gestation.

For practical purposes, the situation in the human being is not actually diverse from that in the macaque, for although the human blastocyst, as has been mentioned above, buries itself in the endometrium and hence thereafter no longer theoretically occupies the uterine cavity, it does in reality effect the anatomic obliteration of the lumen after about the third month.

### Material and Methods

The material used in this study consists of 12 fertilized ova (7 normal and 5 abnormal) discovered in surgically removed uteri at the Free Hospital for Women during the past five years. The clinical group from which these specimens were obtained has been discussed previously,<sup>4</sup> as have also various other clinical, pathologic, and embryologic aspects pertaining to the material.<sup>4-8</sup>

*Procedure.*—The uterus is opened laterally under saline or Locke's solution and the uterine cavity is closely inspected with a four-power binocular dissecting microscope in an effort to recover a free blastocyst.\* The endometrium is then carefully examined under fluid prior to fixation by means of the low-power binocular dissecting microscope. If an implanted ovum is not found, Bouin's fixative is gently pipetted over the endometrial surface while the specimen is still immersed in salt solution, and the endometrium is re-examined with low-power binocular vision.

It is significant that the youngest specimen thus far observed, the 7.5-day ovum, was discovered only after this complete technique had

\*The fluid is pipetted off and examined under the microscope. Also, in the event that the ovum may not yet have entered the uterus, the Fallopian tube corresponding to the ovary containing the most recent corpus luteum is routinely flushed, and the collected fluid is carefully examined in every case.

been employed. The other specimens were found prior to fixation, either with the naked eye immediately upon opening the uterus, or by low-power binocular inspection. Fixation greatly helps to accentuate contours and irregularities of the endometrium and thus serves to reveal the implanted ovum even though the vascular response which would have facilitated detection is not yet discernible by low-power examination of the fresh specimen.

Following fixation for 36 hours in Bonin's fluid, the endo- and myometrium surrounding the ovum may be blocked out into a cube, approximately 15 mm. in all diameters. Some uteri, however, are frontally sectioned after 6 hours so that a slab of endomyometrium, 10 to 15 mm. thick, is removed. This favors fixation of the specimen from below, as well as from above. The ovum, situated near or on the surface, becomes fixed almost immediately, but the deeper parts of the endometrium require longer treatment.

At this point, Doctor Chester H. Henser, of the Department of Embryology of the Carnegie Institution of Washington, takes charge of the material and faultlessly sections the embryo and the adjacent implantation site serially at  $6\mu$ , using the double embedding method of celloidin followed by paraffin. This technique has been described more fully elsewhere.<sup>6</sup>

Each serial section is then photographed by Mr. O. O. Heard on 35 mm. film and enlarged on bromide paper to a diameter necessary for reconstructions. The illustrations for this paper have been kindly prepared by Mr. Chester Reather.

We are greatly indebted to these workers for cooperating in this study, and to Doctors George L. Streeter and George W. Corner for their kind help in interpreting these specimens.

## I. Normal Ova

Table I summarizes the menstrual, coital, and associated pertinent data relating to the 7 normal conceptuses (5 previllous and 2 villous) to be described in the order of age as follows:

### A. Previllous Stages

#### 1. *The 7.5-Day Specimen (Mu-8020)\**

*Low-Power Examination Prior to Section.*—This ovum was discovered by use of the four-power dissecting binocular microscope after partial fixation of the endometrial surface. When its location had been established in this way, it was barely visible to the naked eye, measuring 0.46 by 0.42 mm. After complete fixation, it appeared as a slightly raised, oval area (Fig. 1A) the long diameter of which lay in the vertical axis of the uterus. Within the center of the slightly elevated region was a round opaque zone, the embryonic mass, 0.07 mm. in diameter. When viewed with extremely oblique light, the embryo appeared to be covered by a thin membrane, the abembryonic wall of the ovum. At the periphery, this membrane merged with a thickened opaque rim (Figs. 1B and 1C), the result of trophoblastic development of the ovum where it came in contact with the endometrium.

\*These specimens are designated by letters and numbers, the latter referring to the accession number of the specimen in the Carnegie Embryological Collection.



TABLE I. NORMAL OVA

CASE CARN. NO.* AGE GRAVIDA PARA	MEAN ESTIMATED AGE OF OVUM (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ENDO- METRIAL DATING	DAY OF PROB- ABLE FERTILE COITUS	RANGE OF DAYS ON WHICH CTA. BEGAN	GROSS FINDINGS		LOCATION OF IM- PLANTATION SITE AND OF OVARY CONTAINING ACTIVE CORPUS LUTEUM (C. L.)†
						SIZE AND APPEARANCE OF UTERUS	ENDO- METRIUM	
A: <i>Previllous</i>								
Mu-8020 38 yr. x ix	7.5	24	22	16	28, 32(2 <sup>w</sup> )† 31 (1 <sup>m</sup> )	1½ x enlarged; marked retroflexion	Pale; edematous; 3 to 5 mm. thick; congested and hemorrhagic areas, probably traumatic in ori- gin, at fundus	3 mm. from fun- dus, 7 mm. from left C. L. Right
Wi-8004 29 yr. vi vi	9.5	25	26	15	34 (1 <sup>w</sup> ) 34 (1 <sup>m</sup> )	Slightly enlarged; mod- erately firm; cervix lacerated, everted and eroded; myometrium 20 mm. thick (av.)	Numerous recent petechial hemor- rhages scattered over both sur- faces of endo- metrium	At right cornu 3 mm. from fun- dus, 10 mm. from right uter- ine border C. L. Right
Si-7699 35 yr. iv iii	11.5	25	25	12	26 to 29 (6 <sup>w</sup> )	Cervix moderately erod- ed; myometrium 18 to 22 mm. thick	Pale lavender, ex- cept for congest- ed area around ovum; 3 to 4 mm. thick	In midline, 6 mm. from top of uterine cavity C. L. Left

Re-7950 32 yr. iv	12.0	26	23	13	27 to 33 (7 <sup>w</sup> ) 27 to 35 (6 <sup>m</sup> )	1½ x enlarged; cervix showed moderate circumoral erosion; myometrium 16 to 22 mm. thick	Edematous, pale, lavender-gray; 5 mm. thick (av.)	11 mm. from fundus, 10 mm. from left C. L. Right
Al-7700 34 yr. ix viii	12.5	29	26	15	33 to 36 (4 <sup>m</sup> ) LMP <sup>w</sup>	Markedly lacerated and eroded cervix, with irregularity at the junction of the portio and endocervix; myometrium contained many thickened and tortuous vessels	Pale; slightly convoluted	8 mm. from left, 21 mm. from fundus C. L. Right
<b>B: Villous</b>								
Ra-7801 33 yr. ix vii	13.5	28	26	--§	24 to 28 (4 <sup>w</sup> ) 24 to 28 (8 <sup>m</sup> )	Slightly enlarged; myometrium normal except for thickened, tortuous vessels on cut surface	Lavender to bluish-gray; surface somewhat irregular; 5 to 6 mm. thick	20 mm. from fundus, 10 mm. from right C. L. Right
Ra-7802 37 yr. ix	16.5	33	28	16	26, 33 37, 42¶ (4 ? w or m) LMP <sup>w</sup>	1½ x enlarged	1 cm. area of erosion on anterior portion of endocervix	10 mm. from left, 16 mm. from fundus C. L. Right

\*The accession numbers of the Carnegie Institution of Washington are used to designate these specimens.

†Parentheses enclose number of cycles studied; w indicates menstrual dates were from a written record; m indicates menstrual dates were from memory.

‡All normal ova were found on the posterior wall of the uterus.

§There were no accurately recorded coital dates in this case.

¶The long cycles occurred following birth of baby (7 months preceding operation).

The latter, in general, had a "chicken-skin" appearance, due to the prominent gland mouths interspersed along the flattened, stretched-out epithelial surface. This picture was in marked contrast to that of older endometria (associated with ova seen in Figs. 2A to 7A) which tend to assume a progressively developing so-called "pig-skin" appearance, the appellation given to full-blown decidua.

*Sectioned Specimen.*—The ovum at this stage consists of a superficially but well-attached flattened blastocyst the trophoblast of which has proliferated only at the embryonic pole where the ovum is in contact with the endometrium. It should be noted here, as will be borne out in all specimens described subsequently, that trophoblast develops only where it has adequate contact with maternal tissue. The endometrial epithelium is absent (probably digested) at the implantation site. Damage to the immediately adjacent epithelium is evidenced by the clear, hydropically degenerated nuclei at the junction of the ovum and the surface epithelium. (The surface epithelium is not completely regenerated until about the nineteenth or twentieth day of ovular development, or until approximately a week after the first missed period.)

There is a slight vascular response to the presence of the recently implanted ovum. The endometrium, as noted in Table I, is in the twenty-second day of its cyclic development (Fig. 1B).

(a) *Trophoblast.*—The trophoblast appears as a thick, saucer-shaped mass composed of two main types of cells, the *syncytiotrophoblasts* and the *cytotrophoblasts*; there are also transitions between these two varieties (Fig. 1C). The abembryonic pole of the ovum still consists of the thin, flattened, mesothelium-like cells which characterize the wall of the primate blastocyst prior to implantation.<sup>9</sup> This type of cell metamorphoses rather abruptly into the large polyhedral form seen at the margin of the trophoblastic disc. In the monkey blastocyst, this initial metamorphosis, just after implantation, results in a syncytium, but from the human material available, the nature of these first changes in man is not entirely clear. Apparently, however, the process is quite similar in the human being, because many of the least differentiated cells at the junction of the blastocyst wall have indistinct boundaries and resemble a syncytium, although others possess definite membranes.

i. *Syncytiotrophoblast.*—The syncytiotrophoblast, comprising the bulk of the trophoblastic disc, is peripherally situated and is composed of cells of widely variegated appearance. The earliest form is apparently the single, massive, deeply staining cell with an extremely large and hyperchromatic nucleus. A pair of such cells is seen at the extreme right in Fig. 1C. Various transitions are found between this type of

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Fig. 1.—The 7.5-day ovum, Mu-8020. A. A gross view of the specimen and surrounding endometrium, photographed under fluid. The mouths of the endometrial glands are evident as tiny dark spots, each of which is surrounded by a concentric circle. The superficially implanted ovum appears in the center of the picture as a light opaque ring containing the embryonic mass. The dark ring around the embryo represents the chorionic cavity, while the opaque outer ring represents the double layer of trophoblast at the periphery of the ovum, due to collapse of the blastocyst (See Fig. 1C). X35.

B. A general medium-power view of the recently implanted ovum and associated endometrium. The latter is in the twenty-second day of its cycle (morphologically) and shows active secretion of glands and marked physiologic edema of its stroma. X100.

C. A detailed view of the mid-cross section of the ovum and underlying endometrium. The ovum is well attached by its trophoblast at the embryonic pole, although it is so shallowly implanted at this stage that almost half the ovum is exposed and therefore still shows the characteristics of the blastocyst wall at the abembryonic pole. The primitive character of the trophoblast is evident; the large, dark multinucleated masses represent primitive syncytiotrophoblast, whereas the relatively small, light discrete cells represent the primitive cytotrophoblast. The embryo is the globular mass in the center of the flattened, chorionic cavity and shows the primitive endoderm above and the primitive ectoderm below. The primordium of the amniotic cavity is the tiny cleft between the primitive ectoderm and the trophoblast. X300.

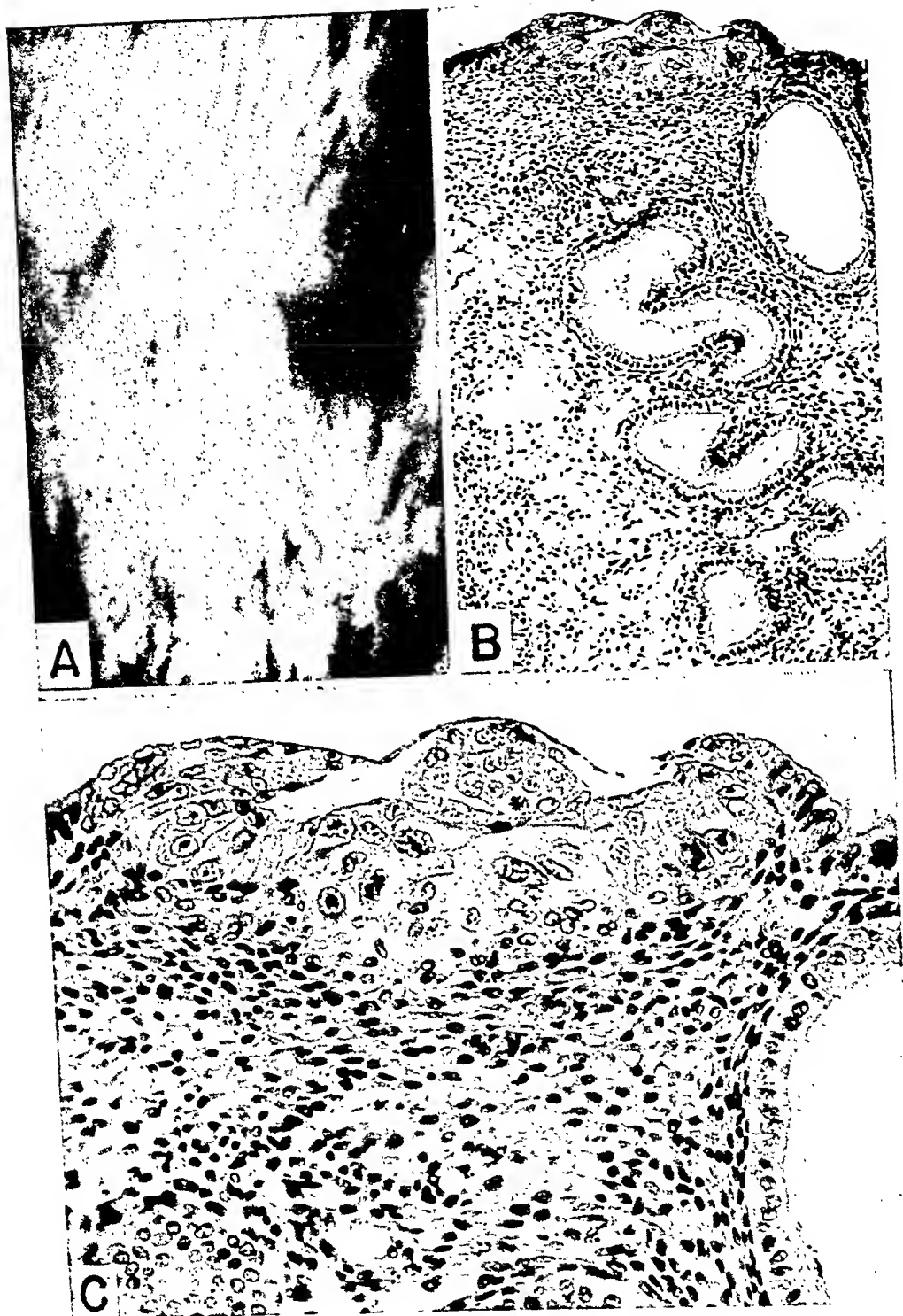


Fig. 1.—For legend see opposite page.

cell and the enormous, dark syncytium containing numerous pleomorphic nuclei lying just beneath the embryonic mass (Fig. 1C). The large hyperchromatic nuclei are the progenitors, whereas the smaller, more mature, nuclei are descendants, apparently derived by amitotic division, since no mitoses are evident anywhere in the syncytiotrophoblast.

The syncytiotrophoblast presents a very uneven surface to the adjacent endometrial stroma. The latter is being invaded by irregular trophoblastic pseudopodia which are in the process of surrounding and digesting small masses of the stroma—presumably to nourish the growing ovum. Two such localized areas of endometrium are seen in Fig. 1C.

ii. *Cytotrophoblast*.—The cytotrophoblast, on the other hand, is much less prominent and consists of large, irregular, pale staining, polyhedral cells lying nearest the chorionic cavity (the cavity of the ovum). Their cell boundaries are distinct in contrast to those of the mature syncytiotrophoblast, although the initial stage in the formation of the latter is a single, large, dark cell. Whether the syncytiotrophoblastic cell is a modified cytotrophoblastic cell or whether both types develop independently when trophoblast first forms after implantation, remains to be determined by further investigation.

(b) *Embryo*.—As seen in Fig. 1C, the embryo proper consists of a flattened globular mass composed of two types of cells: (i) the small dark ones of the superficially situated primitive endoderm; and (ii) the larger, pale, polyhedral cells of the ectoderm. Within the latter germ layer, is a cleft-like amniotic cavity the maximum diameter of which is 24 $\mu$ .

*Age of Ovum and Time of Nidation*.—Since the single and therefore unquestionably fertile coitus in this case took place 7.5 days prior to laparotomy, the conceptus cannot be older than this time interval, although it may be younger.\* The latter, however, is not likely in view of its developmental age. Since the trophoblastic growth may have been going on for possibly as long as 48 hours, embedment may be tentatively estimated to have occurred in a 5.5-day old embryo, or on the sixth day of development. The endometrium at the time of implantation would then have been in the twentieth day of its cyclic development. On the basis of comparative studies, we had not been led to expect that nidation could take place so early, for, in the monkey, Streeter and his co-workers<sup>9</sup> had reported its occurrence on the eighth or ninth day of ovular development.

\*This is in the event that at the time of coitus ovulation had not yet taken place, and that therefore fertilization was delayed pending the release of the egg.

Fig. 2.—The 9.5-day ovum, W-8004. A. A gross surface view of the implantation site photographed under fluid. The ovum is now fairly well implanted; the dark, irregularly oval area in the center represents the exposed portion of the ovum, whereas the opaque peripheral ring represents the portion of the ovum covered by endometrial epithelium. Elsewhere the latter is becoming wrinkled with resulting obliteration of gland mouths.  $\times 22$ .

B. A medium-power view of the now fairly well-implanted ovum and underlying endometrium. The latter, in the twenty-sixth day of its cycle, shows moderate pre-decidual change of its stroma and a "saw-toothed" contour of its secretory glands.  $\times 100$ .

C. A detailed view of a mid-cross section of the ovum and its immediately surrounding endometrium (same section as Fig. 2B). Some epithelial repair of the implantation site has occurred, although a portion of the ovum is still exposed. The prominent feature of the trophoblast, at this stage, is the presence of many anastomosing lacunae within the syncytiotrophoblast. The latter is surrounding and eroding maternal sinusoids which will supply blood to the trophoblastic lacunae. The embryo, still a bilaminar germ disc, shows a moderately well-developed amniotic cavity (below) which is being enclosed by amniogenic cells being derived from, and still attached to, the adjacent trophoblast.  $\times 200$ .

## 2. The 9.5-Day Specimen (Wi-8004)

*Low-Power Examination Prior to Section.*—Upon inspecting the uterine lining, a tiny, raised, red spot, 0.28 mm. in diameter, was discovered, situated as noted in Table I. Around two-thirds of this central point there appeared a zone of brilliant red hemorrhage and/or congestion, the total diameter of the area measuring 0.85 mm.

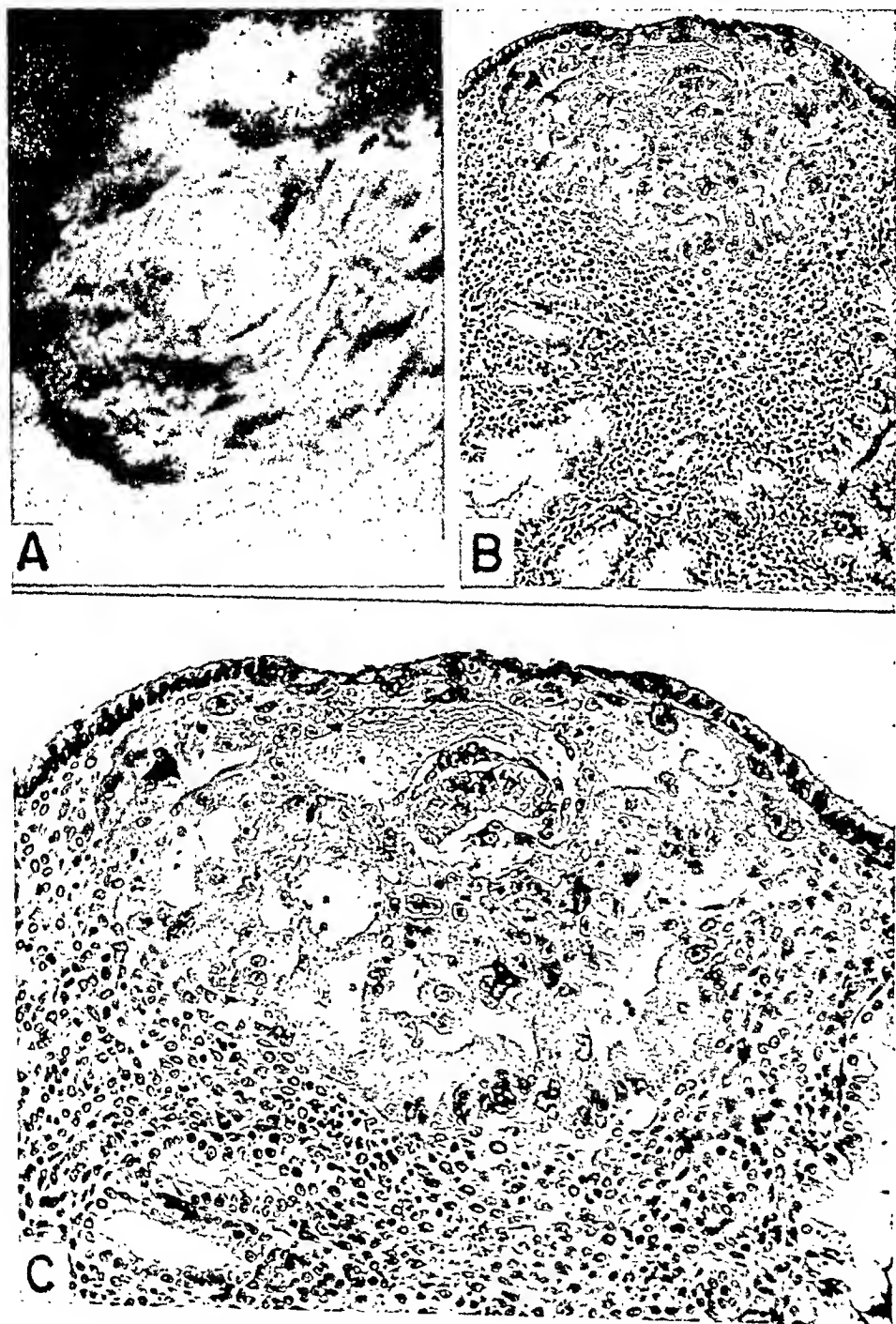


Fig. 2.—For legend see opposite page.

After complete fixation, the implantation site (Fig. 2A) showed an oval, raised area, 1.0 by 0.69 mm. in diameter, the long axis of which was parallel to that of the interstitial portion of the right tube. This elevation rose 0.26 mm. above the surrounding endometrium; at its apex an oval defect in the endometrium, 0.36 by 0.21 mm. in diameter, exposed the ovum immediately underlying the surface. The elevation, therefore represented the partially implanted conceptus over which the endometrial epithelium had begun to regenerate.

The surrounding endometrium was much more mature than that associated with the 7.5-day ovum previously described. The surface was markedly wrinkled and the mouths of the glands were represented by small, irregular slits.

*Sectioned Specimen.*—The embryo at this stage is approximately two-thirds implanted, the defect in the endometrium being partially epithelialized. There are no recognizable elements of the original blastocyst remaining, as was the case in the 7.5-day conceptus; i.e., the thin abembryonic wall.

The endometrium is typical of the twenty-sixth day of cyclic development (Fig. 2B), except that the degree of secretory activity is greater than is encountered in the corresponding stage of the non-pregnant menstrual cycle. This finding agrees with Sturgis'<sup>10</sup> observations of hypersecretory activity in early pregnant endometria. In response to the presence of the ovum, vascular sinusoids are developing from branches of spiral arterioles. The predecidual, or early decidual reaction is only slightly more marked immediately around the ovum than elsewhere (Fig. 2B).

(a) *Trophoblast.*—While the entire wall of the ovum shows some degree of trophoblastic development, this is naturally more prominent at the embryonic than at the abembryonic pole (Fig. 2C).

i. *Syncytiotrophoblast.*—The most conspicuous feature of the trophoblast is the presence of numerous syncytiotrophoblastic lacunae which receive the maternal blood and constitute the future intervillous space of the placenta. Most of these lacunae are intercommunicating, while a few small ones are still isolated. Several of them already contain maternal blood conveyed to the ovum by the developing endometrial sinusoids. In one instance, a lacuna is seen to have ruptured into the chorionic cavity, allowing the escape of maternal blood therein. This feature, while pathologic, is probably not significant. It accounts for the tiny red spot observed in the fresh specimen. Likewise, the area of hemorrhage partially surrounding the central red point was due to the presence of maternal blood in the trophoblastic lacunae. Later on, during the eleventh and twelfth days of development, most of the lacunae become filled with blood which appears as a brilliant hair-line circle around the periphery of the ovum, especially when the latter is superficially implanted.

ii. *Cytotrophoblast.*—The cytotrophoblast is relatively insignificant at this stage and consists of the irregular layer of cells immediately about the chorionic cavity. These are in the process of forming a few primitive mesoblasts, the forerunners of the placental connective tissue elements, vascular as well as supportive. This stage in both the human being and the monkey has been described in some detail by one of the authors (A. T. H.)<sup>11</sup> in 1935.

(b) *Embryo.*—The embryo, or germ disc, while still of bilaminar form with its ventrally situated plate of primitive entoderm and its

dorsally located ectoderm, does show some advance over the younger stage. The amniotic cavity is more pronounced and appears as a space dorsal to the embryo proper.\* The amnion, as in the 11.5- and 12.5-day specimens, is arising in situ from the adjacent cytotrophoblast.

*Age of Ovum.*—On the basis of the degree of development, the probable fertile mating took place 9.5 days prior to operation. Correlation of other subsequent coital dates with the degree of development shows that the conceptus cannot be older than 9.5 days, but it may be slightly younger, if the ovum were not available for immediate fertilization after insemination.

### 3. The 11.5-Day Specimen (Si-7699)

This ovum, as well as the 12.5-day stage (Al-7700) has already been described in detail by the authors,<sup>6</sup> but they are included in this report in order to present in full the various phases of previllous ovular development illustrated by the material available in our study as a whole.

*Low-Power Examination Prior to Section.*—The ovum appeared as an oval, translucent spot, 0.84 by 0.91 mm. in diameter, with its long axis parallel to that of the uterus (Fig. 3A).

The endometrium overlying the ovum rose 0.14 mm. above the general endometrial surface and showed an irregular, cross-like defect from which exuded a tiny, clear mass of coagulum (Fig. 3B). Surrounding the ovum was an irregular, hemorrhagic and/or congested area of endometrium measuring 6.0 by 2.0 mm., a mirror image of which appeared on the anterior wall opposite the implantation site. This was probably due to some local action of the trophoblast on the endometrium. Following fixation, these features, with the exception of the hemorrhage about the ovum, were all accentuated. The endometrium showed stellate crevices representing gland openings with the intervening surface epithelium beginning to wrinkle. The wrinkling is apparently related to the degree of predecidual reaction beneath the surface.

*Sectioned Specimen.*—The ovum is almost entirely buried beneath the endometrium, epithelial regeneration over it having nearly been completed.

The endometrium at the implantation site is 4.25 to 5.0 mm. thick, and, except for the presence of moderate persistent edema, is typical of the twenty-fifth day of the cycle. The spiral arterioles are very prominent, especially near the ovum (Fig. 3C); this is due partly to their dilatation and partly to the surrounding predecidua. There is slight predecidual reaction beneath the epithelium and about the conceptus. The latter has elicited a moderate vascular reaction which on reconstruction, takes the form of an anastomosing network of sinusoids derived from the surrounding arteriovenous capillary system. The circulation at this stage is essentially a one-way phenomenon; that is, terminal capillary twigs from the anastomosing branches drain into the lacunar network, but there is as yet neither arterial nor venous connection with the lacunae of the trophoblast.

#### (a) *Trophoblast.*—

i. *Syncytiotrophoblast.*—The greater portion of the trophoblastic wall is now composed of a thick peripheral shell of syncytiotrophoblast containing numerous blood-filled lacunae, most of which anastomose

\*The ova are all purposely arranged upside down in the illustrations so that the endometrium is oriented in the usual fashion.



with one another. The few lacunae which have not, as yet, become incorporated into this system are those associated with trophoblast in the process of actively eroding contiguous maternal vessels. When the blood from such a vessel flows into a lacuna, the latter acts as a tiny check lock to prevent it from immediately entering the lacunar system, which it does eventually when the lacuna coalesces with its fellows. This would appear to be a safer mechanism than erosion of blood vessels with resultant direct flow of blood into the lacunar system.

ii. *Cytotrophoblast*.—The cytotrophoblast is beginning to be more prominent at this stage and appears as an inner lining of the shell of the ovum. Irregular thickenings of proliferating cytotrophoblast, the first primordia of chorionic villi, are commencing to push peripherally through the outlying syncytiotrophoblast.

(b) *Exocoelom of the Embryo and the Chorionic Cavity*.—The cavity within the ovum has now resumed the essentially spherical shape comparable to the segmentation cavity of the blastocyst prior to implantation. This cavity is called the *exocoelom* of the embryo, whereas the larger space outside, within which lies the embryo, is the *chorionic* cavity.

Lining the exocoelom of the embryo and attached to the entoderm of the germ disc, is a mesothelium-like membrane, first described by Heuser.<sup>12</sup> Beneath this membrane, the significance of which is not as yet understood, are numerous primitive mesoblastic cells, containing a few angioblasts, which represent the forerunners of the connective tissue elements of the placenta.

(c) *Embryo*.—The embryo proper still consists of a bilaminar germ disc, a fairly well-formed amniotic cavity, and an amnion that is still attached to the adjacent trophoblast from which it is arising.

*Age of Embryo*.—While fertile coitus most likely took place on the twelfth day of the cycle, 12.5 days prior to operation, the probable fertilization or developmental age is approximately 11 days, an estimate more in harmony with the embryologic development of the specimen, as well as with the probable time of ovulation in this particular patient.

#### 4. The 12.0-Day Specimen (Re-7950)

*Low-Power Examination Prior to Section*.—The implantation site appeared in the form of a tiny red circle, 0.78 mm. in diameter, within which was a slightly bulging, transparent gray vesicle 0.43 mm. in diameter. The hemorrhagic ring represented the blood within the trophoblastic lacunae, and the vesicle represented the chorionic cavity.

Fixation revealed a shallow 0.23-mm. ulceration in the endometrial epithelium overlying the implanted ovum (Fig. 4A). The latter barely elevated the endometrium in this region. After the specimen had been

Fig. 3.—The 11.5-day ovum, Si-7699. A, A portion of the posterior uterine wall, natural size, to show the implantation site with its surrounding zone of congestion and hemorrhage.

B, A high-power view of the endometrial surface of the implantation site. Note the opaque elevation made by the underlying ovum and the coagulum escaping from the defect in the epithelium. This triangular break in the surface is being repaired by maternal epithelium (See Fig. 3C).  $\times 22$ .

C, A medium-power view of a section through the center of the embryo. The ovum is now well implanted and the epithelial defect nearly repaired (it is completely so in this section). The shell of the ovum is composed of an outer syncytiotrophoblast and an inner cytotrophoblast that is proliferating primordia of chorionic villi. The embryo, still a bilaminar germ right of the implantation axis. The amniotic cavity, the space between the two layers of the embryo, is more advanced than in the 9.5-day specimen. The exocoelomic cavity to the edge of the germ disc, is formed from the primitive connective tissue (mesoblast) lining the chorionic cavity of the ovum.  $\times 100$ .

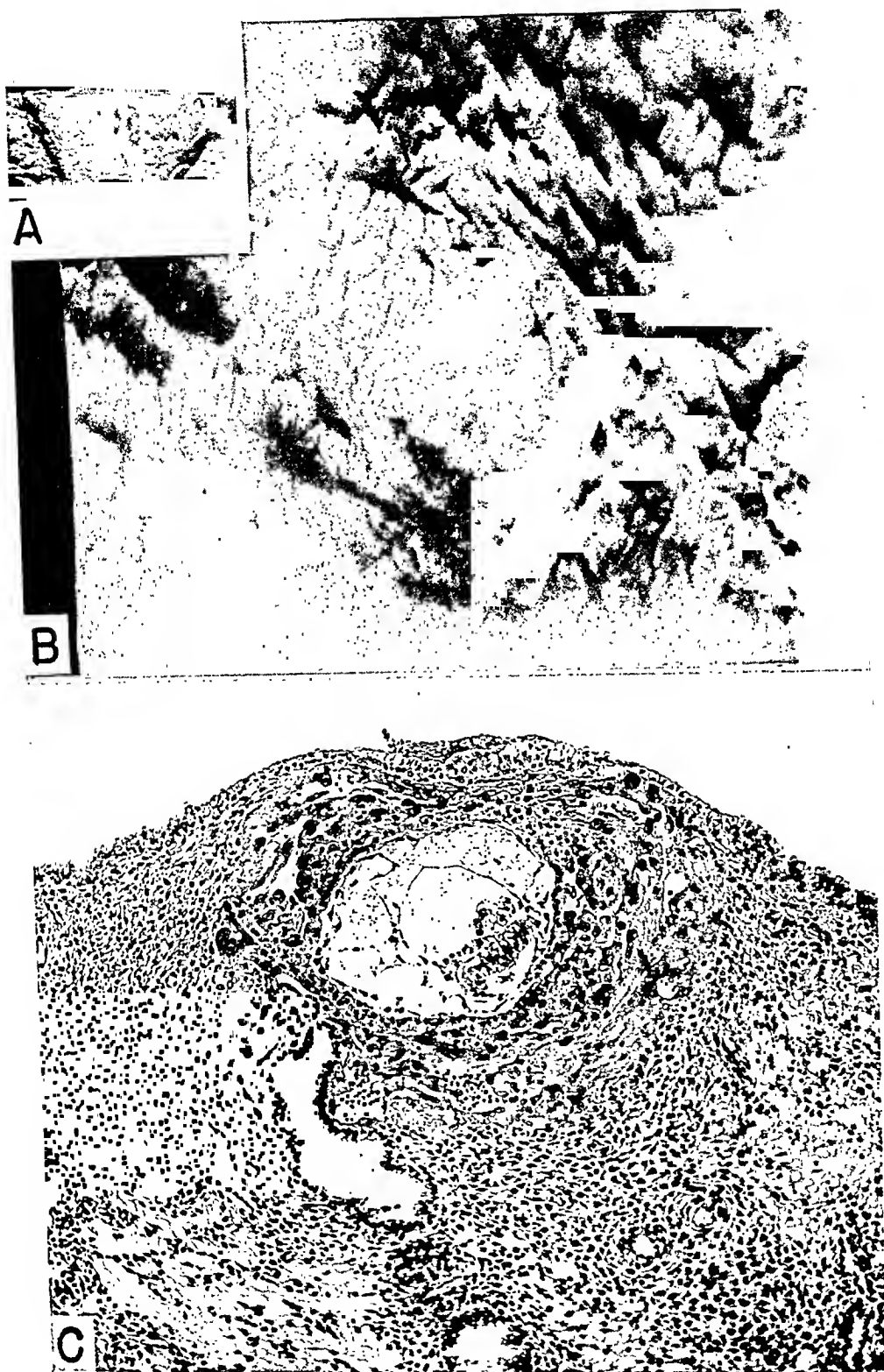


Fig. 3.—For legend see opposite page.

embedded in celloidin and cleared in cedar oil, the implanted ovum was distinctly visible, as shown in Fig. 4B. The vacuolated areas in the thick, peripheral shell represented the trophoblastic lacunae which were filled with maternal blood and which had been visible in the fresh specimen. The large, central cavity—the chorionic cavity of the ovum—had been observed before fixation as a gray, translucent vesicle.

The endometrium elsewhere showed evidence of edema with prominent gland mouths and a slightly bulging epithelial surface between the latter. The edema suggested a comparatively young secretory endometrium, in spite of the relative developmental maturity of the ovum.

*Sectioned Specimen.*—While the ovum is fairly well embedded, the epithelial regeneration of the superficial defect is comparatively scant. This specimen is a little larger and slightly more developed than the preceding one. Aside from the increase in size, the trophoblast is somewhat more mature—the lacunae are larger, more numerous and contain slightly more blood. The few primordia of the chorionic villi are also a bit more advanced in their development. The exocoelom is more mature, but the embryo itself, while in general similar to the previous specimen, is a little less differentiated, judging from the somewhat disorderly arrangement of its ectodermal cells. The germ disc, slightly asymmetric in form, is thicker at one edge than at the opposite one; the significance of this difference is not understood at the present time.

The endometrium, which is in the twenty-third day of its cyclic development, shows no predecidual reaction, in spite of the probable presence of the ovum for approximately 4 to 5 days. The conceptus has, however, elicited a moderate vascular response around itself. The glands are actively secreting, although this feature is poorly illustrated in the particular region photographed because of the edema and the relative scarcity of glands.

*Age of Embryo.*—The probable fertile coitus took place on the thirteenth day of the cycle, 12.5 days prior to operation. There were several subsequent coital dates within the estimated ovulation time, but had conception resulted from any of these, the ovum would have been younger than its obvious developmental age which is intermediate between the 11.5- and 12.5-day specimens; this conceptus has accordingly been dated as 12 days old.

### 5. The 12.5-Day Specimen (Al-7700)

*Low-Power Examination Prior to Section.*—The ovum appeared as a tiny translucent vesicle, slightly less than 1 mm. in diameter, in the midst of a hemorrhagic and/or congested area 7.0 by 10.0 mm., situated as recorded in Table I. At the periphery of the tiny vesicle was a brilliant, 0.9 mm. hair-line red circle representing the maternal blood within the trophoblastic lacunae.

Fig. 4.—The 12.0-day ovum. Re-7950. A. A surface view of the implantation site (photographed under fluid). The ovum is situated beneath the oval ulcer, just above the wedge-shaped area of endometrium.  $\times 22$ .

B. A comparable view of the implantation site after the specimen had been cleared. The ovum is clearly seen in the center of the photograph as a white, ring-like object. The central portion represents the chorionic cavity, while the peripheral portion is the trophoblastic shell containing lacunae.  $\times 22$ .

C. A mid-cross section of the ovum and surrounding endometrium. The former is in essentially the same stage of development as the ova Si-7699 (Fig. 3C) and Al-7700 (Fig. 5B). The endometrium, however, is much younger; i.e., 23 days, instead of 25 and 26 days, respectively. The ovum, therefore, either implanted at a younger stage of its development or on endometrium that was less mature than those of the above-mentioned specimens.  $\times 100$ .

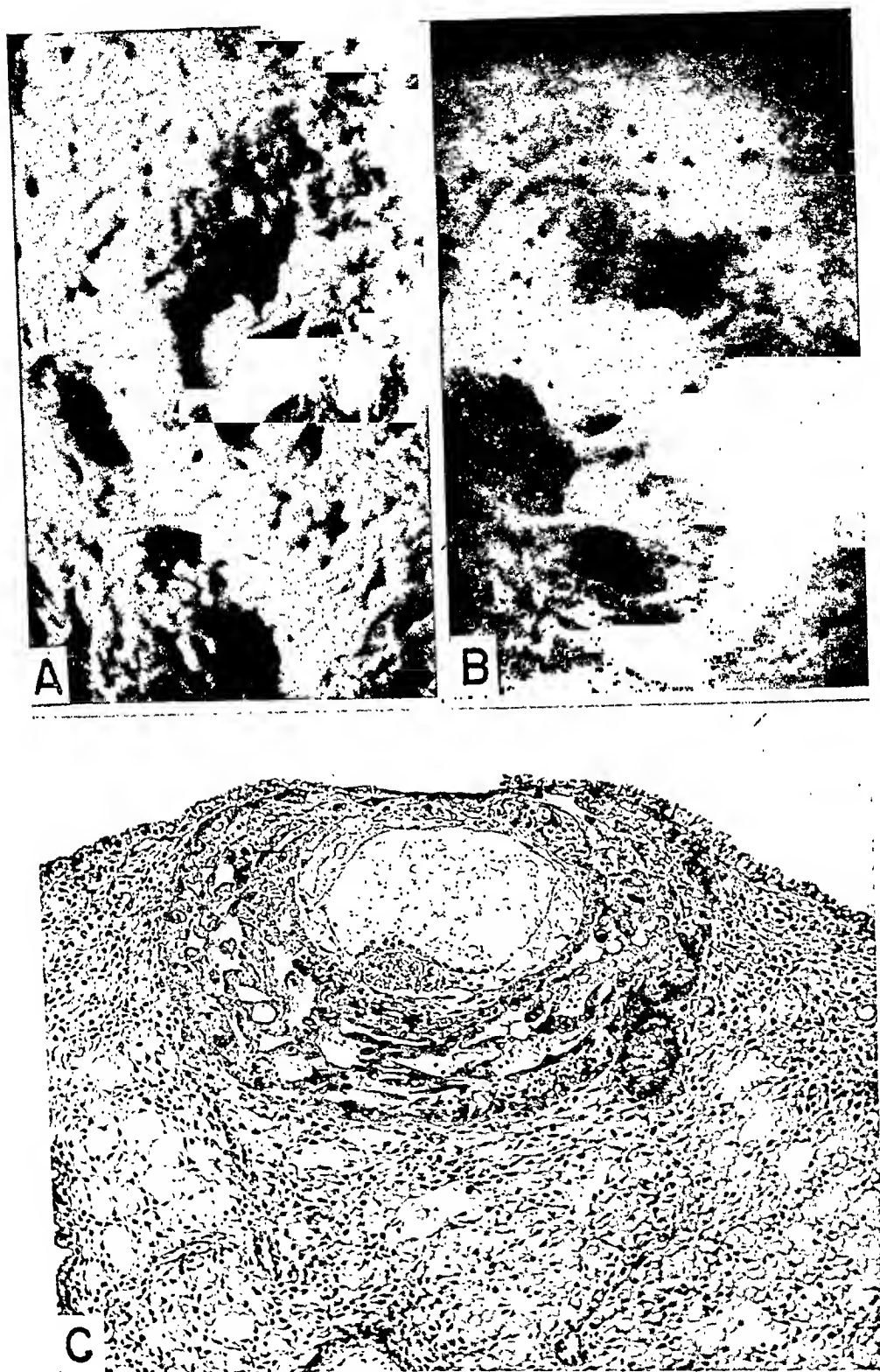


Fig. 4.—For legend see opposite page.

After fixation, the vesicle (Fig. 5A) measured 1.26 mm. in diameter and was raised 0.1 mm. above the surrounding endometrium. The latter showed fine wrinkling of its epithelial surface between the stellate crevices of the gland mouths.

*Sectioned Specimen.*—The ovum (Fig. 5B) is slightly more advanced in its development than the 12.0-day stage, although the embryo proper is not significantly different. The egg is less deeply implanted and hence not as completely covered by regenerating maternal epithelium. Indeed, some of the overlying tissue is necrotic, probably as a result of interference with its blood supply by the ovum underneath.

(a) *Trophoblast.*—Correlated with a more superficial implantation is a relatively poorly developed abembryonic trophoblast.

i. *Syncytiotrophoblast.*—Elsewhere the trophoblast shows large, well-filled lacunae within the peripheral syncytiotrophoblast.

ii. *Cytotrophoblast.*—The cytotrophoblast now assumes a more active role. Prominent primordia of chorionic villi, arising from the inner cytotrophoblastic shell, are growing superficially through the surrounding syncytiotrophoblast to lay the foundation for the primitive villous stage.

The endometrium, which is characteristic of the twenty-sixth day of development, shows edema, as well as a moderate predecidual and secretory reaction. Near the conceptus, the sinusoids of the endometrium are prominent and slightly congested. Hemorrhage has occurred in the endometrial stroma from nearby sinusoids, many of which have definite defects in their endothelial lining. A fairly early decidual reaction is present in the stroma about the ovum and shows mild leukocytic infiltration.

*Age of Embryo.*—The single and therefore undoubtedly fertile coitus took place on the fifteenth day of the cycle, 13.5 days prior to operation. Therefore the conceptus cannot be older than 13.5 days. On the basis of its morphologic development, its age has been estimated as approximately 12 to 13 days.

## B. Villous Ova\*

Two examples of the primitive villous stage (Ru-7801 and Bu-7802) will be briefly described in order to trace the development of the villous ova up to a more familiar phase of chorionic development. Also these specimens will serve for comparison with one of the pathologic ova (Br-7800) which failed to develop chorionic villi because of some defect in the trophoblast.

\*These two ova are being described in detail by Doctor C. H. Heuser, of the Carnegie Institution of Washington, Department of Embryology, for publication in the near future.

Fig. 5.—The 12.5-day ovum, Al-7700. A. A surface view (under fluid) of the implantation site. This specimen is relatively shallowly implanted, as compared to the three previous ones (Figs. 2-4), and hence the ovum creates a more prominent elevation of the endometrium. Some of this prominence is, however, due to increasing maturity of the ovum, as also seen, for example, in the 13.5-day specimen (Fig. 6).  $\times 22$ .

B. A mid-cross section of the ovum and surrounding endometrium. This specimen differs from the two preceding ones (Figs. 3 and 4) in that the primordia of the chorionic villi are more fully developed. Such primordia are best seen at "4" and "8 o'clock" as proliferation . . . . . An increased amount of maternal blood is present in the . . . . . future intervillous space). The early decidual reaction at . . . . . ore advanced than in the 11.5-day specimen (Fig. 3C).  $\times 100$ .

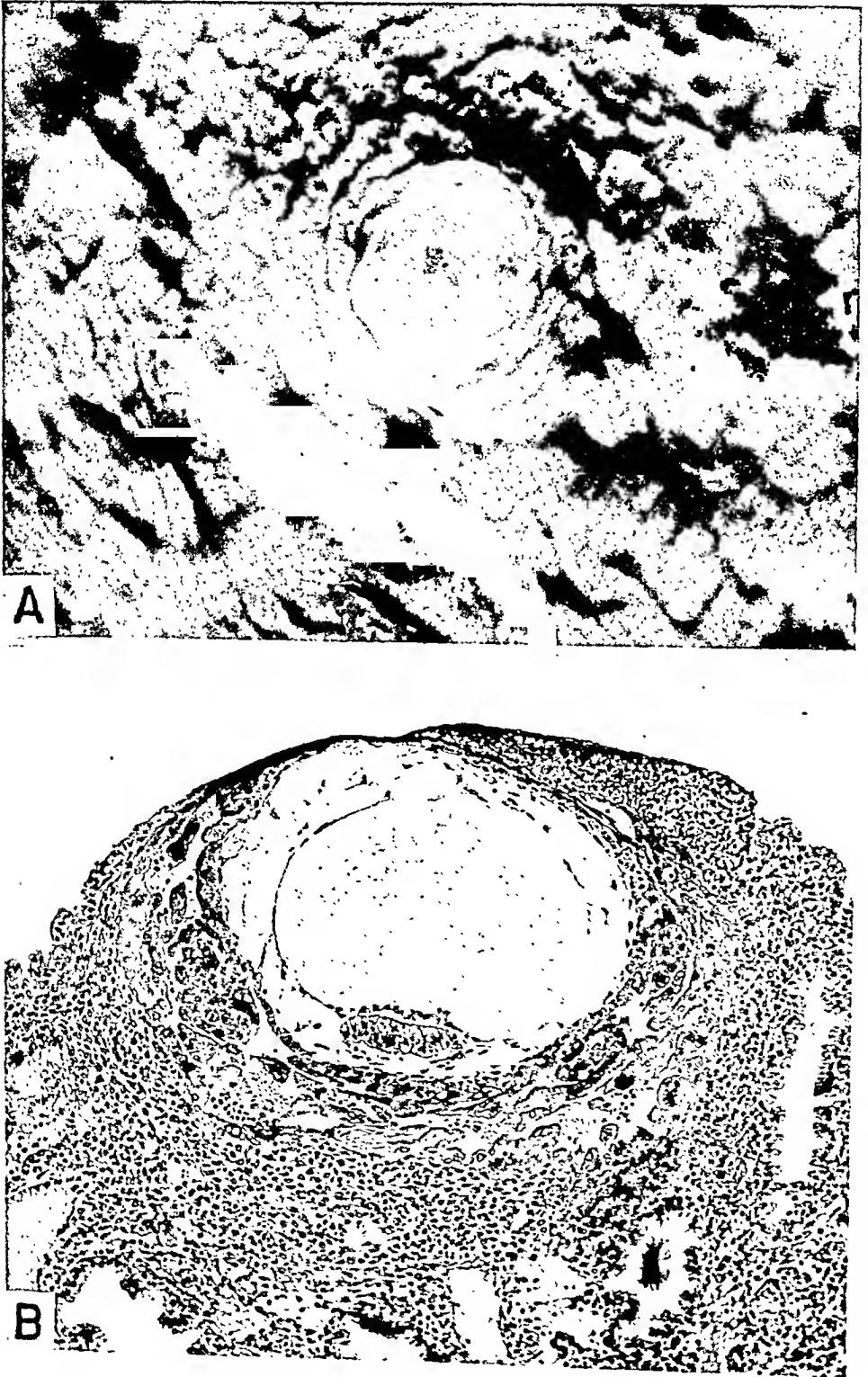


FIG. 5.—For legend see opposite page.

### 1. *The 13.5-Day Specimen (Ru-7801)*

*Low-Power Examination Prior to Fixation.*—In the fresh specimen, the implantation site appeared as a somewhat conical elevation 3.6 by 3.06 mm., surmounted by a hemorrhagic roughened area, 1.8 by 2.16 mm., from which issued a bright hemorrhagic tab measuring 2.0 by 3.0 mm.

There was no hemorrhage or congestion in the surrounding endometrium, as had been the case in both the 11.5- and the 12.5-day specimens.

After fixation (Fig. 6A), these various features were accentuated, except for color changes. The roughened, hemorrhagic area could now be seen to be due to a cap-like formation of fibrin and old blood clot, the so-called "Schlussoagulum" of Peters.

The epithelial surface of the endometrium disappeared under the overhanging edge of this cap, much as the skin disappears under the edge of a moderately old scab. The surrounding endometrium showed a coarsely but irregularly convoluted surface with numerous fine wrinkles and fairly prominent stellate gland openings. The gross picture of the endometrium was suggestive of early or developing decidua.

#### *Sectioned Specimen.*—

(a) *Development of Chorionic Membrane.*—The most prominent feature in this ovum (Fig. 6B) is the formation of simple unbranched chorionic villi from the irregular framework of cytotrophoblast which is clothed by the syncytiotrophoblast lining the intervillous space. Active growth of the cytotrophoblast toward the periphery of the ovum is apparently displacing the remnants of syncytiotrophoblast. The latter are beginning to appear in the surrounding decidua as placental site giant cells. This portion of the implantation site has been investigated in both man and the macaque by Ramsey.<sup>13</sup>

There is now a distinct chorionic membrane composed of the outer syncytium and the inner Langhans' epithelial layer. The latter is adjacent to the prominent mesoblastic layer lining the chorionic cavity. In situ angio- and mesogenesis are still active in the mesenchymal tips of growing villi and, to a lesser extent, on the inner surface of the chorionic membrane.

The endometrium of the implantation site shows marked vascular response to the presence of the conceptus (Fig. 6B) in the form of large, thin-walled sinusoids containing relatively little blood. Hemorrhage has occurred into a dilated gland beneath the ovum, due to erosion of the epithelium by the trophoblast, followed by reflux bleeding from the intervillous space. There is marked, early decidual response about the ovum. Associated with this altered stroma, are infiltrating, placental site giant cells derived from the cast-off, early, peripheral syncytiotrophoblast. The surface epithelium is attempting to close in

Fig. 6.—The 13.5-day ovum, Ru-7801. A. The surface view (under fluid) of the implantation site. The endometrium is now beginning to assume the "pigskin" appearance of decidua. The completely implanted ovum is covered by an operculum, or "Schlussoagulum," from which fresh maternal blood is escaping. The latter is seen as the irregular tab to the right of the elevation made by the ovum.  $\times 8$ . B. A mid-cross section, low-power, of the ovum and surrounding endometrium. The chorionic villi have formed, and are either simple in type or show early branching. A considerable amount of maternal blood is within the intervillous space, having gained access therein from vessels not appearing in this photograph, as well as from the large, dilated sinusoid seen at the left. The blood beneath the ovum is within a gland, due to communication of the latter with the intervillous space. The decidua around the ovum contains many placental site giant cells, derived from the "desquamated" cells of the primitive syncytiotrophoblast. The embryo, deviating to the right of the implantation axis, now has a well-developed amnion (to the right) and yolk sac (to the left). The operculum is shown above the ovum.  $\times 35$ .





Fig. 6.—For legend see opposite page.



the defect created by the implanting ovum, but much of the embryonic pole of the latter is devoid of any covering except the "Schlusseoagulum." Beneath this is a relatively large blood space, the intervillous space, the maternal blood from which has seeped out through and under the "Schlusseoagulum" to cause the hemorrhage seen in the fresh specimen. Elsewhere, the endometrium is actively secretory, vascular, and in the stage of early but definite decidual formation about the spiral arterioles and beneath the surface epithelium.

(b) *Embryo*.—The embryo has now assumed its more familiar form and possesses a typical yolk sac and amniotic cavity. The epithelial portion, or embryonic shield, however, still consists only of a dorsal ectoderm and a ventral yolk sac entoderm.

The amnion, in places, is double-layered, as is the yolk sac, but no hematopoiesis is present in the wall of the latter. The exocoelomic membrane (Heuser's) has disintegrated, leaving several vesicular fragments within the chorionic cavity. It is thought by some (Heuser<sup>14</sup>) that this membrane is the primitive precursor of the yolk sac and that the latter is in some way, as yet not fully understood, derived from it. Others, including the authors, believe it to be merely the lining of the chorionic cavity, or, conversely, the boundary of the exocoelom, derived from the primitive mesoblastic cells lining the chorionic cavity.

*Age of Ovum*.—There were no accurately recorded coital data, but, on the basis of its morphology, this specimen, which is similar in its general development to the famous Peters' ovum, was estimated to be between 13 and 14 days of age.

## 2. The 16.5-Day Specimen (Bu-7802)

*Low-Power Examination Prior to Section*.—In the fresh, the ovum was seen as a slightly oval, raised, plateau-like area, measuring 5.0 by 6.0 mm. The elevated portion was slightly translucent and presented a finely mottled, hemorrhagic and/or congested appearance. Surrounding the raised area, was a collar of bright red surface hemorrhage varying from 0.7 to 2.0 mm. in width (Fig. 7A).

Following fixation, the "Schlusseoagulum," or closing cap, could be readily distinguished and measured 3.96 by 5.4 mm. The edges were curled up and the epithelium of the adjacent endometrium disappeared beneath the scab-like structure. The recent hemorrhage arose from beneath the edge of the latter.

The endometrium showed a moderately coarse irregularity of its surface which in general was markedly wrinkled. Gland openings were not as prominent as in previous specimens.

### *Sectioned Specimen*.—

(a) *Chorion*.—The ovum now possesses early branching chorionic villi attached to a well-defined and moderately mature chorionic membrane (Fig. 7B). Discontinuous vascular primordia are present in the

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Fig. 7.—The 16.5-day ovum, Bu-7802. A. The surface view (under fluid) of the implantation site showing the operculum, recent hemorrhage, and the early decidual reaction of the endometrium. X6.

B. A mid-cross section of the ovum and its surrounding endometrium. This specimen differs from the preceding one (Fig. 6) in that the chorionic villi are more complex and the maternal vascular response more pronounced. Note the large, vascular sinusoid in the lower left-hand corner of the photograph. It is striking that there is comparatively little blood in the intervillous space in comparison to the size of the sinusoidal system that will ultimately supply the ovum with blood. The embryo has now lost its bilaminar character and shows what appears to be primitive streak formation with early mesoderm formation. The yolk sac is more advanced and possesses a double wall. Between the amnion and the chorion is a mass of mesenchyma—a potential amniotic duct. X30.



Fig. 7.—For legend see opposite page.

TABLE II. ABNORMAL OVA

CASE CARN. NO. AGE GRAVIDA PARA	MEAN ESTI- MATED AGE OF OVUM (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ENDO- METRIAL DATING	DAY OF PROBABLE FERTILE COITUS	RANGE OF DAYS ON WHICH CTA. BEGAN	SIZE AND APPEAR- ANCE OF UTERUS	ENDO- METRIUM	GROSS FINDINGS	
								LOCATION OF IM- PLANTATION SITE AND OF OVARY CON- TAINING ACTIVE CORPUS LUTEUM (C. L.) †	
Be-7771 35 yr. iv iv	--*	32	27	--*	30 to 32 (3 <sup>w</sup> )	Laceration, eversion and erosion of cervix	Polypoid; congest- ed; 5 mm. thick (av.)	2.5 cm. from fundus and at the ex- treme right mar- gin of the uterine cavity C. L. Left	
Tr-7700 28 yr. vi vi	11.5	31	25	18	31, 33 (2 <sup>w</sup> ) 31, 37, 41 (m)	1½ x enlarged; cer- vix lacerated, everted and erod- ed, with moderate irregularity of the junction between portio and endo- cervix	Thick (6 mm.); pale, edematous; lavender-gray; moderate numbers of irregular, stel- late depressions 1 to 2 mm. in depth and 1 to 3 mm. in diam. which re- sembled scars	Near right cornu, 10 mm. from fundus and 7 mm. from lateral boundary C. L. Right	
Er-7850 33 yr. xv xi	11.5	31	25	18	32, 34 (m)	Not remarkable	4 to 6 mm. thick; lavender-pale gray	13 mm. from fun- dus, 11 mm. from right C. L. Left	
Sm-8000 29 yr. v iv	11.5	28	25	16	32, 32 (2 <sup>w</sup> )	Normal	Pale yellow; 5 mm. thick; areas of hemorrhage sug- gesting impending cta.	15 mm. from fun- dus, 5 mm. from left C. L. Left	
Br-7800 35 yr. iv iv	13.5	32	26	--†	25 to 31 (3 <sup>w</sup> )	1½ x enlarged; cer- vix lacerated	5 to 6 mm. thick; gray; undulating; many coarse, ir- regular erevices and fissures be- tween undulations	15 mm. from fun- dus, 8 mm. from right border of uterine cavity C. L. Right	

\*Because of the extreme abnormality of this ovum and the large number of coital dates recorded, there is no way of accurately estimating the day of probable fertile coitus or the age of the egg which may be anywhere between 11.5 and 17.5 days.

†All abnormal ova were found on the anterior wall of the uterus.

‡Owing to the large number of coital dates, as well as the abnormal condition of this specimen, the day of probable fertile coitus cannot be estimated.

mesoblastic connective tissue of the chorion and its villi. The cytotrophoblast at the tips of the villi shows more progress in its peripheral growth toward the goal of ultimately forming a new shell of trophoblast to replace the early peripheral shell of syncytiotrophoblast. It would appear that the cytotrophoblast through this phase of villous formation follows the syncytiotrophoblastic framework which was formed earlier by the vacuolization of the solid syncytiotrophoblast.

Microscopically, the endometrium about the ovum, as elsewhere, shows an increasing vascularity and decidual reaction, as compared to the preceding specimen.

(b) *Embryo*.—The embryo shows some progress over the previous stage; the primitive streak is present and true mesoderm is forming. There are suggestions of vessels in the wall of the rapidly maturing yolk sac. The amnion is attached to the chorionic membrane by what appears to be an amniotic duct primordium.

*Age of Ovum*.—The degree of development of this conceptus is compatible with the assigned age of 16.5 days which would place conception on the third coital date recorded within the estimated ovulation time. Since, however, intercourse also took place 2 days before and 2 days after this date, the exact fertilization age cannot be established.

## II. Abnormal Ova

Having outlined briefly the main features typical of the 7 early normal ova, we will go on now to consider the principal characteristics of the 5 pathologic ova recovered in the course of our investigation. No attempt will be made to assign definite developmental ages to these specimens, for, since in every case, one or more of their component structures is pathologic or even absent, it is difficult to estimate accurately their absolute or even their relative ages. However, the specimens will be described in the order of their apparent developmental ages, on the basis of clinical as well as available embryologic data. Other pertinent information relating to these specimens is summarized in Table II.

### 1. *A Previlious Ovum With Defective Trophoblast and Absent Embryo (Be-7771)*

*Low-Power Examination Prior to Section*.—Before fixation, the implantation site appeared as a tiny, polypoid structure approximately 1.0 mm. in diameter. On the tip of the polyp was a hemorrhagic mass 4.0 mm. in diameter, the base of which was extremely vascular. Aside from these features, it did not differ from several other polyps present in the uterus. Whether the ovum implanted in a polyp, or whether the implantation site became polypoid, is difficult to determine. Probably the former occurred, since the endometrium largely surrounds the ovum and the latter is above the general level of the endometrium. At any rate other polyps were present, and it is conceivable that an ovum could attach itself to such a structure.

During the process of dehydration which followed fixation, the hemorrhagic portion became detached from the tip of the implantation site (Fig. 84). The polypoid area now measured 1.07 by 0.8 mm. in diameter and was elevated 1.07 mm. above the endometrial surface.

The endometrium, characteristic of the mature stage, showed stellate crevices of gland mouths and moderate fine wrinkling of the intervening surface.

*Sectioned Specimen.*—The ovum (Fig. 8B) is a mere trophoblastic shell, and by no means a perfect one. The chorionic cavity is extremely small and shows abortive attempts to form mesoblast and possibly also a Heuser's membrane. There is moderate cytotrophoblast formation, but the syncytiotrophoblast is scanty with excessive dilatation of the lacunae. The maternal blood has begun to clot within the lacunae; this probably represents the initial step in the cutting off of nutriment to the ovum which would eventually have led to its death. The syncytiotrophoblast in contact with endometrium is negligible in amount and shows none of the activity one associates with this tissue. Indeed, it seems largely to have degenerated, resulting in deposition of fibrinoid material. Similar material is deposited in degenerating trophoblast associated with maturation of the placenta and in hydatidiform moles.

The endometrium was characteristic of the twenty-seventh day of the cycle, and showed moderate predecidual development, physiologic leucocytic infiltration, and secretory exhaustion of its glands. In the absence of pregnancy, menstruation would undoubtedly have occurred very soon, and it might even have taken place in spite of the pregnancy, because of the extremely defective condition of the ovum. The predecidua about the ovum is moderately prominent and contains many infiltrating macrophages and a few polymorphonuclear leucocytes.

This specimen is of interest because it gives an insight into the pathogenesis of the largest single group (46 and 48 per cent, respectively, in Hertig's<sup>15, 16</sup> two series) of spontaneously aborted ova, the pathologic or blighted ova, which either contain no embryo, or at most an extremely defective one.

*Age of Ovum.*—There were 4 recorded coital dates within the estimated ovulation time (days 14 through 20 of the cycle). The actual age of the specimen may be anywhere between 11.5 and 17.5 days, although it is probably in its twelfth day of development.

## 2. Slight Hypoplasia of Trophoblast (Tr-7770)

*Low-Power Examination Prior to Section.*—The implantation site appeared as a slightly elevated, oval, hemorrhagic ring, 1.07 by 1.35 mm. in diameter (Fig. 9A). Its center was translucent but showed finely stippled hemorrhagic areas. After fixation, this appearance was found to be due to the epithelial defect created by the ovum. The surrounding endometrium was congested over a zone approximately 10 mm. in diameter. On the posterior wall, corresponding to the position of the implantation site, was a punched-out area, 2.5 mm. in diameter, with a hemorrhagic margin. This was similar to the hemorrhage opposite the implantation site of the normal 11.5-day stage.

Fig. 8.—A pathologic previllous ovum without embryonic rudiment, Be-7771. A. Surface view (under fluid) of the polypoid implantation site. The latter is at the edge of the uterine cavity, the lateral sulcus of which is represented by the diagonal furrow to the left of the ovum. The roughened tissue to the left is the cut surface of the myometrium.  $\times 14$ .

B. A mid-cross section of this defective ovum showing an empty chorionic sac embedded within a polypoid mass of endometrium that has undergone a moderate decidual reaction. Aside from the obvious defect—the lack of an embryo—the ovum presents a marked deficiency of trophoblastic development. The syncytiotrophoblastic element is very hypoplastic and shows marked dilatation of its lacunae.  $\times 100$ .

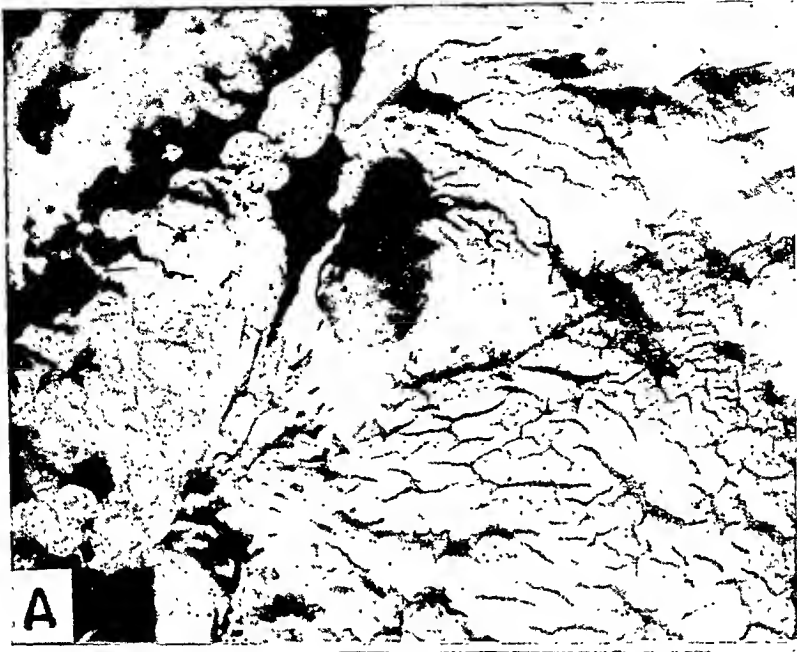


Fig. 8.—For legend see opposite page.

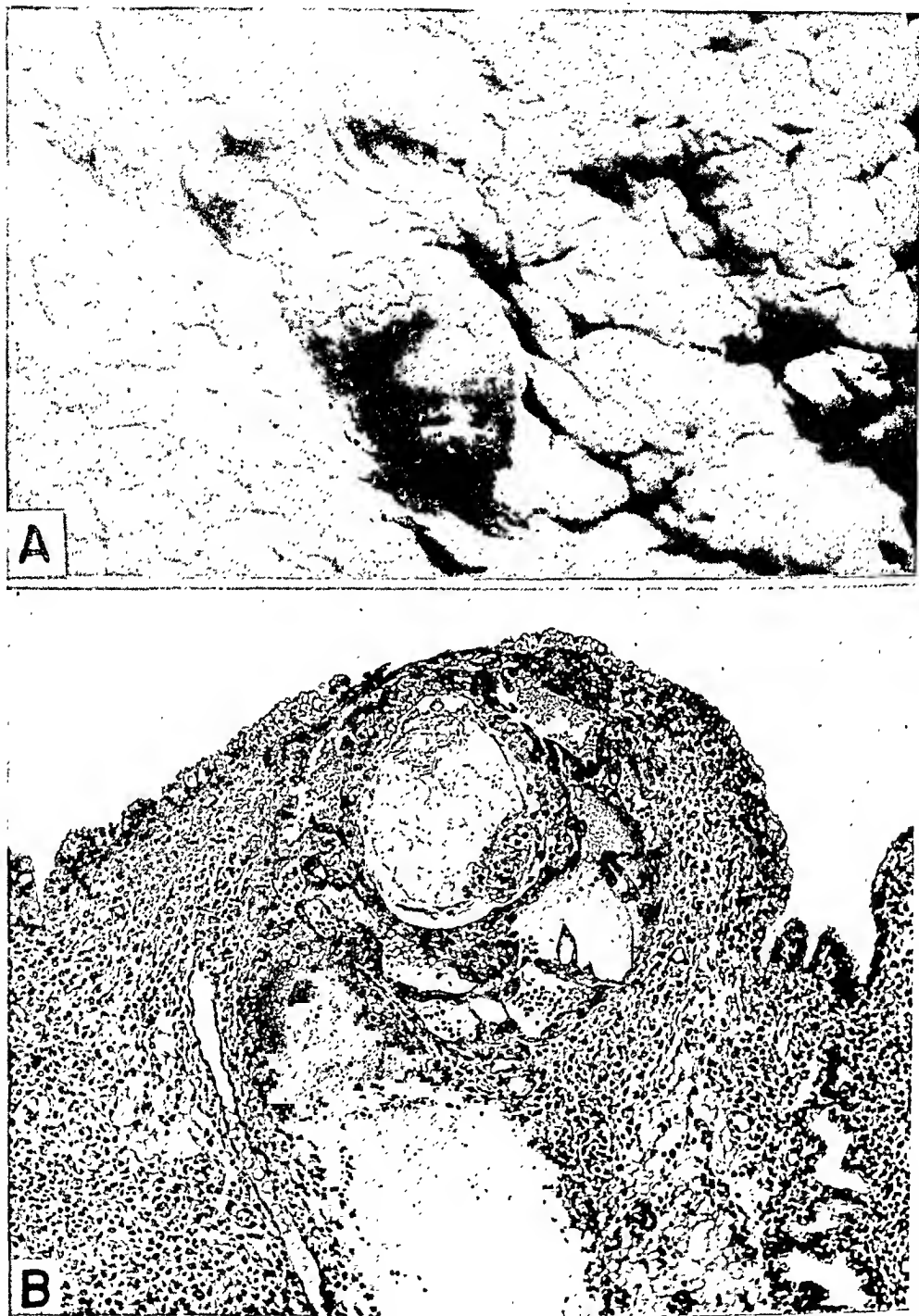


Fig. 9.—A pathologic previllous ovum with slight hypoplasia of the trophoblast, Tr-7770.—A. Surface view (under fluid) of implantation site. The hemorrhagic elevation, with the small, oval ulcer in the center, is caused by the implanted ovum. The endometrium resembles early decidua.  $\times 22$ .

B. A mid-cross section of the ovum and its surrounding endometrium. Although the embryo and the attached exocoelomic membrane are essentially normal, the amount of primitive mesoblast, or connective tissue, lining the chorionic cavity is deficient. The cytotrophoblast is probably within normal limits of development, although the syncytiotrophoblast is moderately hypoplastic. The lacunae are dilated and filled with blood. The hemorrhage below the ovum is within a gland and is not necessarily pathologic, as shown by its occurrence in the normal 13.5-day specimen (Fig. 6B). The endometrium is normal.  $\times 100$ .

*Sectioned Specimen.*—The ovum itself (Fig. 9B) is quite similar to Si-7699, Re-7950, and Al-7700 (Figs. 3C, 4C, and 5B, respectively). However, it is actually smaller than even the youngest of these, although certain features, such as the degree of primordial villous development and of hemorrhage into the trophoblastic lacunae, are quite advanced. The trophoblast appears to be deficient, both relatively and absolutely, particularly with respect to the syncytial element. This deficiency is somewhat reminiscent of the previous specimen, Be-7771 (Fig. 8B), although not to such a marked degree.

The relative lack of primitive mesoblastic development within the chorionic cavity is also in keeping with the hypoplasia of the trophoblast, since the latter gives rise to this future chorionic connective tissue. Within the exocoelom there is some deposition of fibrin, the source of which is not evident.

*Embryo.*—The embryo is not remarkable except for its somewhat eccentric position, a feature observed in 2 of the normal specimens, Si-7699 and Ru-7801 (Figs. 3C and 6B).

The endometrium, typical of the twenty-fifth day of the cycle, showed saw-toothed, secreting glands, moderate predecidual reaction, and some dilatation of the vessels. In the neighborhood of the ovum, edema was fairly prominent, with early predecidual reaction, some recent hemorrhage, and slight leucocytic response. Vascular sinusoids were fairly prominent but often devoid of erythrocytes. Hemorrhage has occurred into an eroded gland similar to that seen in Fig. 6B. The endometrial epithelium is defective over approximately one-half the implantation site with consequent direct exposure of the underlying trophoblast.

*Age of Ovum.*—The probable fertile coitus took place on the eighteenth day of the cycle, 12.5 days prior to operation. An additional coital date recorded on the twenty-seventh day of the cycle is most likely not significant. The assigned developmental age of approximately 11.5 days is in keeping with the clinical history, as well as with the similarity of this conceptus to the 3 normal specimens of this general age group.

### 3. *Hypoplasia of Trophoblast (Er-7850)*

*Low-Power Examination Prior to Section.*—In the fresh specimen, the implantation site appeared as a crescent-shaped, hemorrhagic area, approximately 1.0 mm. in diameter, surrounded by a tiny, pearl-gray elevation which showed slight congestion or hemorrhage.

After fixation, the implantation site measured 1.44 by 1.62 mm. and was elevated 0.35 mm. above the endometrium (Fig. 10A). The "Schlussoagulum," with its characteristic mottled hemorrhagic appearance, was plainly visible, as was also the crescent-shaped area of hemorrhage; the latter, seen previously in the fresh specimen, was due to blood in the trophoblastic lacunae.

*Sectioned Specimen.*—The most prominent feature of this pathologic ovum is the extreme dilatation and congestion of the trophoblastic lacunae (Fig. 10B). The syncytiotrophoblast is very hypoplastic, its substance being reduced to a relatively few tiny, irregular strands lying between the hypoplastic chorionic membrane and the thin peripheral shell of degenerated syncytiotrophoblast. Curiously enough, the best cytotrophoblastic development, as well as the correlated mesoblast formation, is seen on the abembryonic pole where the maternal blood supply is least abundant. The lacunae are directly continuous



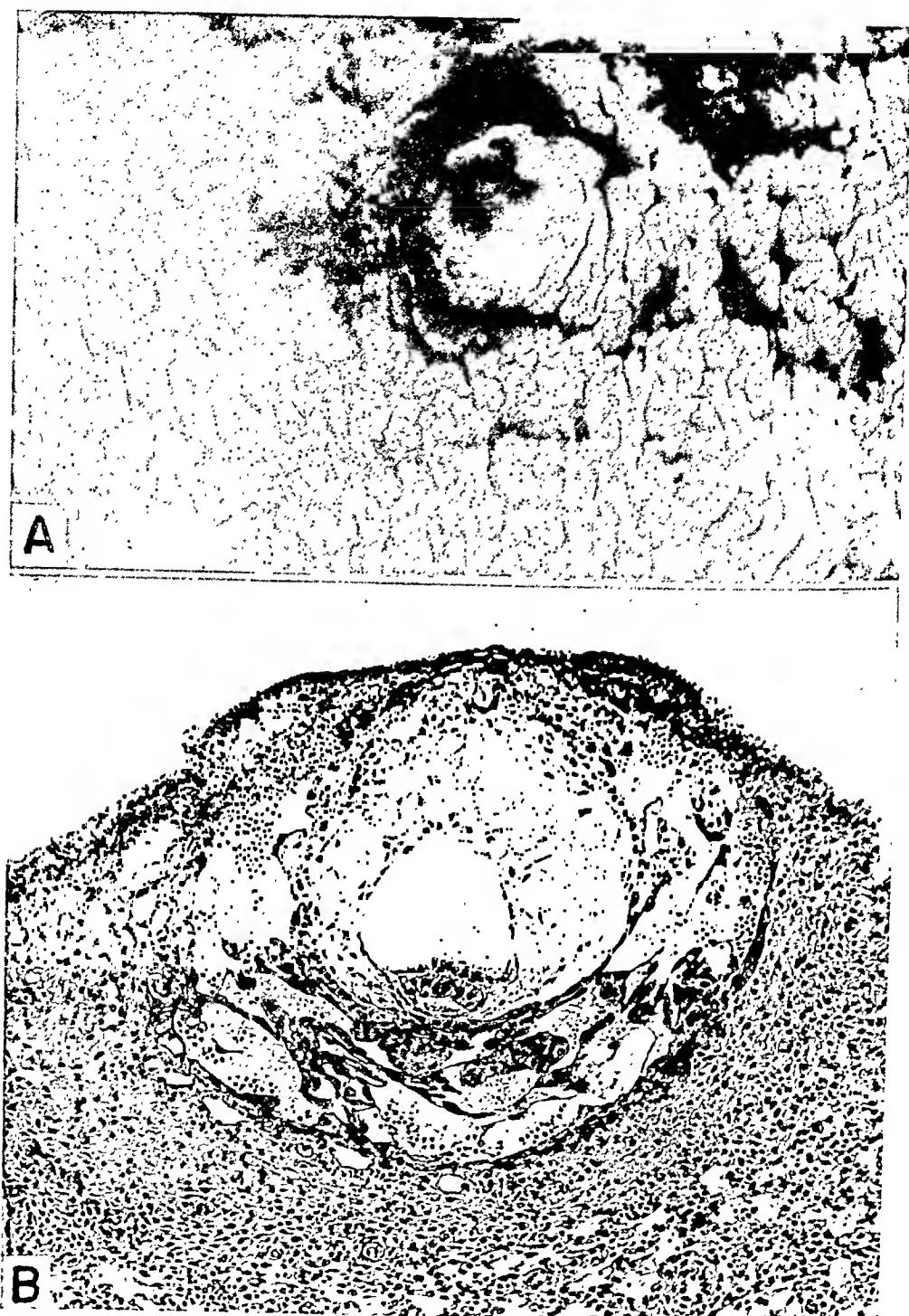


Fig. 10.—A pathologic previllous ovum with slight hypoplasia of the trophoblast, Er-7850. A. Surface view (under fluid) of implantation site. The latter is represented by the hemorrhagic elevation just above the center of the photograph. Partially surrounding the ovum is the crescentic area of hemorrhage and congested endometrium.

B. A mid-cross section of the ovum and surrounding endometrium. The latter shows early decidual reaction. The syncytiotrophoblast is deficient in development and shows accentuation of lacunae containing more blood than usual for this stage of development. The embryo is essentially normal.  $\times 100$ .

with the "Schlussoagululum," and the blood within these spaces has undoubtedly contributed largely to its formation.

The endometrium adjacent to the ovum shows a definite decidual reaction with pronounced leucocytic infiltration. There is moderate vascularity in response to the presence of the ovum, although, in keeping with this general stage of ovular development, the dilated sinusoids contain relatively little blood. Elsewhere, the endometrium is of the late secretory type with an early decidual reaction. There is some edema of the stroma and the vessels are large and congested.

*Embryo.*—The embryo is not particularly remarkable. It possesses a bilaminar germ disc, an amnion and a well-defined exocoelomic membrane. It is slightly smaller than its pathologic contemporary (Fig. 9B), and definitely smaller than any of the 3 normal embryos of a similar stage of development.

*Age of Ovum.*—Since this specimen most nearly resembles the normal 12-day ovum (Re-7950), fertile coitus probably took place on the eighteenth day of the cycle, 12.5 days prior to operation. While coitus was also recorded on the fifteenth and twenty-first days, it seems unlikely that conception occurred on either of these occasions.

#### 4. A Shallowly Implanted Ovum (Sm-8000)

*Low-Power Examination Prior to Section.*—The only evidence of the presence of this ovum was a 2.7 mm. bright red hemorrhagic mass of polypoid shape (Fig. 11A).

The endometrium, after fixation, was characteristic of the late secretory phase; the surface was finely wrinkled with only slightly prominent stellate crevices made by the mouths of the glands.

*Sectioned Specimen.*—The striking feature of this ovum is the shallowness of its implantation (Figs. 11B and 11C). While the trophoblast is fairly normal for the eleventh day of development, one-half of the ovum projects above the endometrial surface and is covered only by the hemorrhage seen in the fresh specimen. As in the previous conceptus (Er-7850), which likewise is imperfectly implanted for its age, the hemorrhagic cap is continuous with the lacunar spaces from which the blood has escaped.

The embryo is not remarkable for this stage of development, nor is the maternal reaction to the conceptus unusual. Here, therefore, is an example of an apparently normal ovum which has become poorly implanted and would probably have aborted in the not too distant future. If abortion did not occur, it is conceivable that such an ovum might lead to the formation of a circumvallate placenta, a condition apparently associated with shallow implantation of an otherwise normal conceptus.

*Age of Ovum.*—The only possible fertile coitus had taken place on the sixteenth day of the cycle, 11.5 days prior to operation. The specimen was accordingly estimated to be 11 to 12 days old.

#### 5. Extreme Hypoplasia of the Trophoblast (Br-7800)

*Low-Power Examination Prior to Section.*—Evidence for the presence of an implanted ovum was seen in a small hemorrhagic elevation 3.78 by 3.42 mm. (Figs. 12A and B). Beneath and to one side of the hemorrhagic portion was a translucent elevated area, 3.0 by 2.7 mm., containing a rounded, bluish spot, 0.7 mm. in diameter. The raised zone represented the ovum, and the bluish spot—the hemorrhage into a gland beneath the ovum (Fig. 12C).

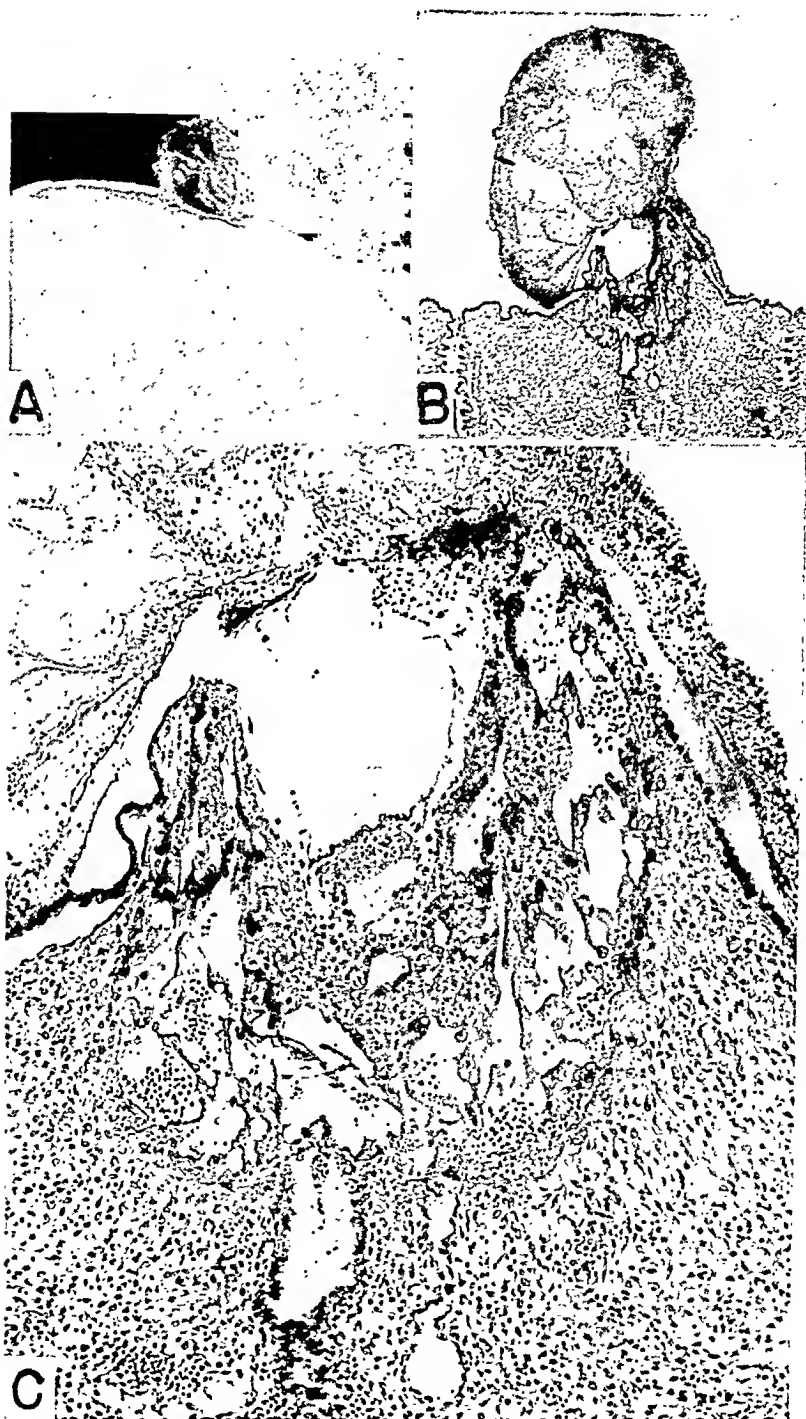


Fig. 11.—A shallowly implanted but otherwise normal ovum, Sm-8000. A. Lateral view of block of endometrium containing the implanting ovum. Note hemorrhage above the implantation site.  $\times 5$ .

B. Low-power view of mid-cross section of implantation site to show the degree to which the ovum protrudes above the surrounding surface. The blood clot occupies the position of the usual operculum.  $\times 20$ .

C. A detailed view of ovum (same section as Fig. 11B). The essentially normal features of the ovum are evident. The break in the abembryonic pole of the ovum is probably a traumatic artefact. For this stage of development (ca. 12 days), the ovum should be well embedded.  $\times 100$ .

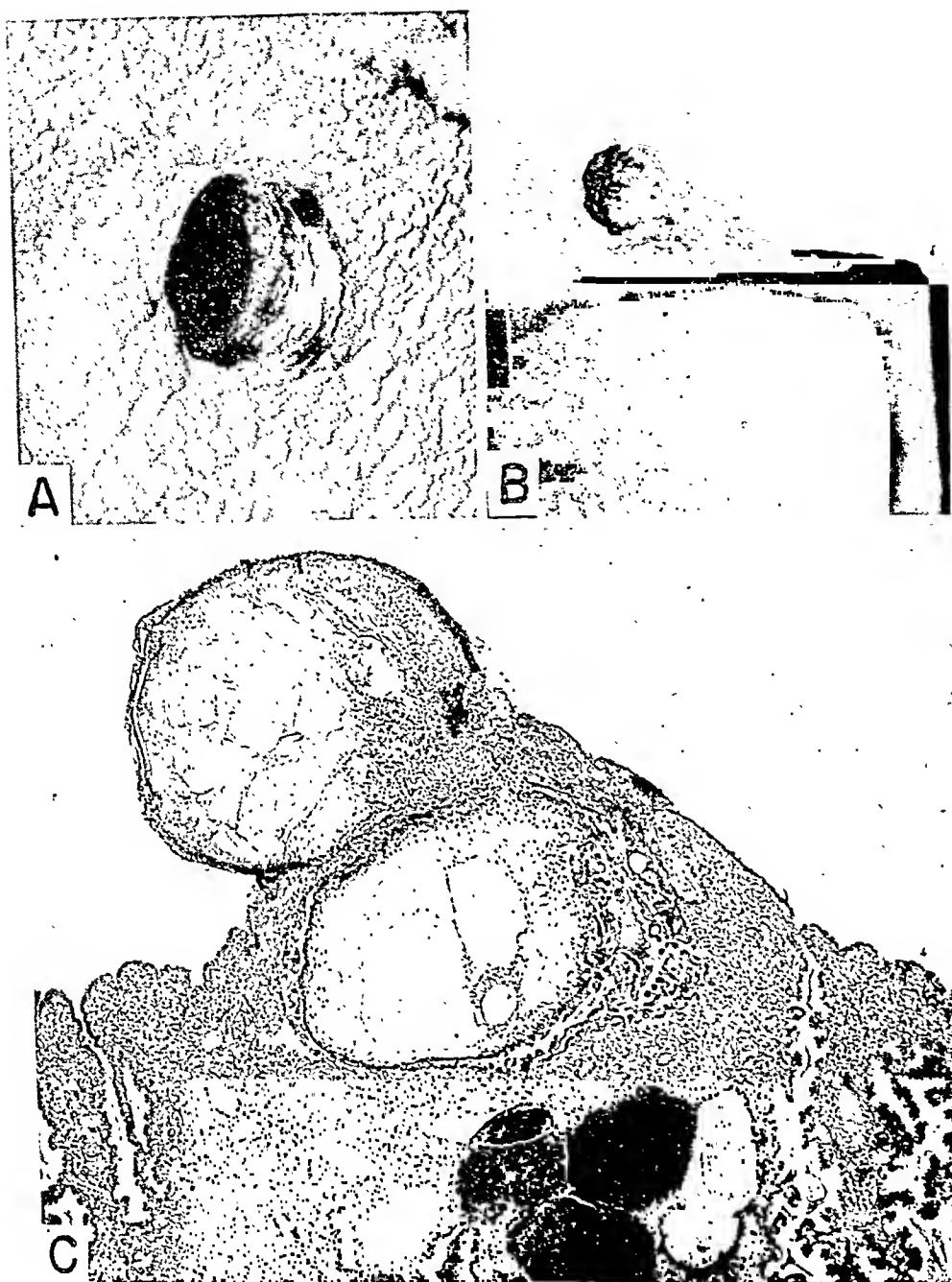


Fig. 12.—A supposedly early villous ovum with extreme hypoplasia of the trophoblast, Br-7800. A. Surface view (under fluid) of implantation site. The most prominent feature is a hemorrhagic mass on top of, and to a large extent replacing, the operculum.  $\times 8$ .

B. Implantation site, lateral view, showing the hemorrhage on top of elevation made by implanting ovum.  $\times 8$ .

C. A mid-cross section of the ovum and surrounding endometrium. The most striking feature in this specimen is the extreme hypoplasia of the trophoblast around three-quarters of the periphery and the marked abnormality of the remaining trophoblast. An ovum containing an embryo in this stage of development (well-developed amnion and yolk sac) should be about 13 to 14 days of age. Compare the degree of trophoblastic development of this specimen with that of the normal 13.5-day ovum (Fig. 6B).  $\times 35$ .

*Sectioned Specimen.*—The principal features of this conceptus are a very deficient trophoblast, but a relatively normal embryonic disc. The exocoelomic membrane has begun to break up and a definitive yolk sac has now formed. Approximately two-thirds of the trophoblastic shell is represented by an indifferent or degenerated syncytium and only a very thin Langhans' layer. The remaining one-third shows abortive attempts at syncytiotrophoblastic formation with lacunae containing maternal blood. No sign of villous formation is present, in spite of the fact that the degree of embryonic development indicates that there should be numerous simple villi at this stage (Figs. 6B and 7B).

The remainder of the implantation site shows an excellent vascular and early decidual response. Hence the maternal environment *per se* does not appear to be abnormal.

It would appear, therefore, that this ovum is definitely defective and that its trophoblast would not long support the growing embryo; hence abortion would probably have occurred in the near future.

*Age of Ovum.*—There are several recorded coital dates, none of which, however, is critical. On the basis of the degree of development shown by the embryonic disc, the developmental age is approximately 13 to 14 days.

### Discussion

Even though the ages of the 5 normal previllous ova encompass a time interval of not more than 5 days, there are still many problems to be elucidated within this particular phase of ovular development, due to the scarcity of material illustrating critical stages. Among the questions that await further investigation, or are worthy of special comment, we may briefly mention the following:

*Differentiation of the Trophoblastic Elements.*—How the two types of trophoblastic cells differentiate is largely influenced by the manner in which the trophoblast responds to its initial contact with maternal tissue. While the two fundamental types of cells appear to be laid down *de novo*, the possibility of their both arising from an indifferent trophoblast that forms immediately upon implantation cannot be entirely ruled out.

*Formation of the Trophoblastic Lacunae.*—The time and mode of formation of the trophoblastic lacunae have not been satisfactorily determined by the study of our material. Whereas very early vacuolization of an occasional syncytiotrophoblastic mass does take place, most of the lacunar development occurs during the eighth and ninth days of growth. That the lacunae are at first isolated and then coalesce to form a functional intervillous space is evident from the specimens representing the tenth to the thirteenth days of development. It is probably significant that the new lacunae formed during these stages are associated with trophoblast that is eroding blood vessels, hence allowing blood to enter the isolated lacuna prior to the latter's coalescence with the main lacunar system. This may possibly serve as a protective mechanism to prevent blood from flooding the entire system at once. After the vessel is adequately connected with the isolated

lacuna, blood flow into the embryonic placenta is quite likely controlled by vascular tone.

*Nutrition of the Ovum.*—It is striking that during the first phase of implantation the trophoblast, and hence the ovum, obtains much of its nourishment from actual ingestion of maternal stroma. This, of course, mechanically facilitates implantation, but it probably is not the only reason for such a process. Even as late as the twelfth and thirteenth days of development there still remain evidences of phagocytosed maternal tissue within the syncytiotrophoblast. It is significant, perhaps, that the most active ingestion of such tissue is prior to the time when the trophoblast is in direct contact with maternal blood.

*The So-Called "Placental Sign" in the Human Being.*—It is interesting that profound vascular disturbance in the endometrium of the implantation site does not occur until about the twelfth day when one encounters, in this series, congestion and hemorrhage. As students, we were taught that hemorrhage probably took place early, and that this facilitated the nourishment of the ovum prior to the establishment of the uteroplacental circulation.

The presence of blood, or coagulum containing blood, on the surface of the implantation site, is worthy of comment because it brings to mind the so-called "placental sign" in the macaque monkey, first described by Hartman.<sup>17</sup> In the human being, it may conceivably be of practical significance in causing miscalculation of the estimated date of confinement, since it occurs at about the time of the first missed menstrual period. The pregnancy in which such hemorrhage, even though scanty, is noticed by the patient and mistaken for a menstrual period, would appear to be one month shorter than is actually the case.

*Repair at the Implantation Site.*—The relative degree of epithelial repair of the defect created by the implanting ovum varies among the specimens, and apparently depends upon the depth of implantation for any given degree of ovular development. Thus the reparative process has progressed to the slightest extent in two pathologic ova which are shallowly implanted.

*Endometrial and Ovular Development.*—The correlation of ovular and endometrial maturity deserves some speculation. On the basis of comparative studies in the macaque, one would expect an 8- or 9-day blastocyst to implant on a 22- or 23-day secretory endometrium, the pattern of which would show relatively little variation in different specimens of this age group. As a sequel to this assumption, one would expect a given stage of ovular development to be associated with a definite corresponding endometrial phase, but such is not always the case. Thus, whereas the 12-day specimen of our series is embedded in 23-day secretory endometrium, the 9.5-day one is associated with 26-day endometrium. There can be only two explanations for such discrepancy: either the ovum implants at a variable stage of its development, or it implants on endometrium that may vary in its degree of secretory development. The

latter may be due to delay in fertilization of the ovum, or to variations in the endometrium itself, on the basis of corpus luteum activity. Probably both factors are concerned in this unexpected picture. Actually in the human being, the single implanted blastocyst available indicates that it can embed at the age of approximately 6 days on 20-day endometrium. The human ovum has also been found to implant as late as the twenty-third day, judging from the 9.5-day specimen, or as early as the eighteenth day, as was the case in the 12-day one. A more extensive series will serve to elucidate this matter.

*Location of Embedment.*—There was no correlation between the position of the implanted ovum and the side on which the corresponding corpus luteum was found. The ovum may embed anywhere in the uterine cavity, irrespective of the ovary of origin. On the other hand, in our limited series there appears to be a definite correlation between the position of the ovum and its condition: the normal ova were, without exception, recovered from the posterior wall of the uterus, while the abnormal ones embedded on the anterior wall. The importance of this finding is probably more apparent than real, since this series can hardly be statistically significant.

*Factors Influencing Condition of Ova.*—From a preliminary survey of the pathologic material among our specimens, it is apparent that various types of abnormality are encountered. Most of them appear to be associated with intrinsically defective ova, although shallow implantation seems clearly to play a part in the pathogenesis of these future abortions. Whether the most defective ovum of the group (Be-7771) became abnormal because it implanted on an endometrial polyp, or whether it was intrinsically abnormal, is impossible to determine. It is certain, judging from at least one of the other specimens (Br-7800, Fig. 12) that the endometrial environment cannot invariably be held responsible for the extreme degree of trophoblastic hypoplasia observed.

### Summary

A series of 5 previllous and 2 villous normal human ova, ranging from 7.5 to 16.5 days in developmental age, shows that the human blastocyst implants on the posterior wall, probably during the late sixth or nearly seventh day of its development, on endometrium that may range from the eighteenth to the twenty-third day of its development. Actually there are no precise data on the time of implantation, since the youngest specimen, and therefore the most critical one with respect to this process, is already implanted. The figures given (late sixth or early seventh day) are deduced on the basis of this youngest specimen. Even younger ova must be secured in order to determine the actual time of implantation.

Trophoblast proliferates at the site of implantation which, at first, consists of solid cyto- and syneytiotrophoblast. The latter becomes vacuolated on the eighth day to develop lacunae for the reception of maternal

blood on about the eleventh day. The chorionic villi begin to form as cytotrophoblastic masses on the twelfth to thirteenth day and grow peripherally along the syncytiotrophoblastic framework, ultimately coalescing peripherally to displace the syncytiotrophoblast, except the portion lining the intervillous space. Remnants of the desquamated syncytiotrophoblast are encountered in the placental site as giant cells.

A series of 5 abnormal previllous ova, the developmental ages of which range from approximately the eleventh to the fourteenth day, but which are difficult to interpret accurately because of their abnormality, shows a variety of conditions ranging from shallow implantation of an otherwise normal ovum, through extreme hypoplasia of the trophoblast, to complete absence of the embryonic mass. The pathologic ova were all found on the anterior wall of the uterus.

#### A. Conclusions.—Normal Ova

1. A series of normal previllous human ova, discovered in uteri removed surgically prior to the first missed menstrual period, is reported.

2. The human blastocyst probably implants during the late sixth or early seventh day of its development on endometrium that may show the characteristics of the eighteenth to the twenty-third day of development.

3. The solid syncytiotrophoblast of the early implanted blastocyst develops lacunae, beginning on the eighth day, which subsequently coalesce and begin to receive maternal blood on about the eleventh day.

4. Chorionic villi form from peripherally growing masses of cytotrophoblast which arise from the chorionic membrane on about the twelfth day.

5. The peripheral syncytiotrophoblastic shell of the previllous ovum is "desquamated" at approximately the same time as the cytotrophoblast of primitive villi makes contact with the decidua.

6. The "placental site giant cells" are the remnants of this desquamated syncytiotrophoblast.

#### B. Conclusions.—Abnormal Ova

1. Five pathologic or pathologically implanted previllous ova, discovered in uteri removed surgically prior to the first menstrual period, are reported.

2. Shallow embedment of one ovum apparently accounts for the abnormality encountered in an otherwise normal nidation site.

3. Varying degrees of trophoblastic hypoplasia are observed in 4 intrinsically pathologic ova.

4. Absence of the embryonic rudiment is seen in an ovum showing faulty trophoblastic development and apparently implanted on an endometrial polyp.



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## THE BLOOD VESSELS OF THE MYOMATOUS UTERUS

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IN 1912 John A. Sampson<sup>1</sup> published a paper about the blood supply of uterine myomas. There is no other similar study of the subject in the English language. This fact, if there were no others, would seem to warrant a review of the matter.

The blood supply of myomas is obviously related to some of their degenerations; to the reasons why some myomatous uteri bleed while others do not; and finally there are interesting questions to be answered by one familiar with Sampson's work as to the nature of the circulation of the individual tumor. For example, in general, he found each myoma a mass of proliferating arteries and in most instances could demonstrate few if any veins within the tumor substance. Sampson never believed this to be an injection fault and his opinion is apparently correct. Therefore, the mechanics of arteriovenous exchange in myomas is perhaps capable of clearer visualization than in his work. In a personal letter last year, also, Sampson kindly expressed another problem to be checked: namely, whether in his injections—since he did not measure injection pressure he might have overinjected the arteries and perhaps have filled the lymphatics—that being a possibility in this type of anatomical work.

This paper does not propose to answer all of the questions of tumor degenerations and uterine bleeding but is the presentation of anatomical material obtained by the use of an injection medium new for this purpose, which allows the direct study of the blood vessels of the uterus and the myoma.

Sampson's work, as well as that of Bardon<sup>2</sup> in France, and Holmgren<sup>3</sup> in Stockholm, was done by injection of the myomatous uterus with colored gelatin, the pigment being either plain or radiopaque. Cross slices of the specimens were studied and stereoscopic radiographs made of some cross slices injected with radiopaque material. An accurate picture of the circulation was thereby obtained in most instances from these preparations for, when properly made the blood vessels stood out plainly in the radiograph against the faint background of the specimen. However, the composite picture of the blood supply was always obtained indirectly, i.e., from study of stereoscopic radiographs. In the use of this method there were many problems to be worked out as to proper x-ray exposure and in obtaining radiographs from the proper angles to show the vessels, because nobody could tell beforehand except in a general way, where the major vessels were going to be. Many such technical problems were avoided by the present method of study.

There are several anatomical methods available for the direct study of blood vessels, but most are difficult to use or at best result in incomplete injections. Because of some previous experience with synthetic liquid latex, hereafter for brevity called "Neoprene," this substance was used as the injection medium. This material in the original state is a thin, milky fluid which needs only to be filtered to be ready to use. It does not have to be warmed nor does the specimen need to be warmed before injection, or cooled afterwards to set the injection medium. It coagulates instantly in acid which is added to the normal fixative used for the specimen after the injection is complete.

After some trial two proprietary injection compounds of neoprene were chosen for use, one containing red pigment, the other black. The exact pigments in these compounds the manufacturer\* would not disclose. However, it is known that the black pigment does not have a granule size of over 2 microns and the red pigment size is not over 0.4 microns. If it is remembered that the average red blood cell is 7 microns in diameter, it is obvious that neither of these pigments should fail to give a thorough injection. However, granule size is not the only consideration in the completeness of an anatomical injection. Surface tension, vessel spasm, and mutual coagulating action of injection compound and tissues enter into the picture. From experience with neoprene, it is clear that under normal conditions it goes over into but not through the capillary bed. This same conclusion was reached by another worker<sup>4</sup> using these compounds in injections of the kidney.

After injection with neoprene the myomatous uterus was either prepared as a corrosion specimen or cleared by the Spalteholz method. One type of anatomical preparation served as a check on the other.

This material lends itself naturally to the preparation of multicolored corrosion specimens. These are specimens in which after injection the flesh is eaten off with acid leaving only the injected cast of the circulation. Such casts cannot be made after injections with gelatin. When properly obtained with neoprene they resemble a multicolored rubber bath sponge. The routine preparation of corrosion specimens would seem to have the disadvantage that microscopic sections are difficult to obtain without defects in the casts. However, all uteri studied by this method, were cut in half after fixation and only half of the specimen was corroded, or suitable further precautions were taken to protect the patient from whom the myoma was removed. The cervix was amputated and sectioned, since it does not inject in a surgical specimen, and sections were made of any suspicious tumors or suspicious areas in the uterine cavity. The corrosion preparations were uniformly made by injecting the arteries with red neoprene and the veins with black.

Neoprene will tolerate the Spalteholz clearing process which, using slices of a gross specimen, is roughly similar to preparation of a micro-

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\*American Anode, Inc., Akron, Ohio.

scopic section. After injection the tumor is dehydrated in successive alcohols and then cleared in benzol and wintergreen oil. However, it was found that only the black pigment would stand this process without diffusion. Also it was learned very early that both arteries and veins could not be injected for study in the cleared specimen because of the resulting confusion caused by the heavy black injection. For simplicity, also, only uteri containing single or at the most two or three myomas were studied by this method.

The clearing process when properly carried out, though quite time consuming, results in excellent specimens for study of the arterial system.

### Injection Methods

When utilizing surgical specimens it was found necessary, as a rule, to use those removed personally so that proper pedicles would remain for cannulation and undue injury to the tumor avoided during operation. Small glass cannulas (Fig. 3) were inserted into both uterine arteries and veins of the freshly removed specimen and at low pressure the blood washed out by connection to the arterial cannulas. There is a great differences of practice among anatomists in this detail. Washing may be done briefly, not at all, or thoroughly. With this injection medium the most satisfactory injections were obtained after washing the specimen thoroughly with cold tap water for an hour or two, even at the expense of some edema. Thorough blanching of the specimen was thereby obtained. The uterus was then covered and put in the refrigerator overnight and the injection done the next day, there being at this time almost complete disappearance of the edema. During the washing all gross vessels which leaked were ligated. It was found that injection was more difficult if performed later than twenty-four hours for the reason that leaking points previously tied off usually let go, probably from softening of the suture material.

The neoprene injection compound after filtering was introduced into the vessels from a simple pressure bottle to which was connected a mercury manometer. The pressure used never exceeded 180 mm. of mercury for arteries, and 120 mm. of mercury for veins. The end point of injection for arteries was an easy matter because the arterial system filled promptly and the end point could be determined visually, the injection being complete when vessels distant from the point of injection were full. The venous injection was considerably slower and completeness often required some gentle massage of the uterus. When the veins properly filled the uterus turned black, the color of the injection mass, and wherever there was uterine muscle the specimen was slightly swollen and tense. The sensation of filling the venous sinuses of the uterus was that of slowly filling a hot water bottle. During injection small leaks were stopped by sopping with an alcohol sponge.

After injection of one or both circulations, the uterus was placed at once in 5 per cent formaldehyde strongly acidified with acetic acid. When thoroughly fixed, depending on the size of the specimen, from several days to several weeks, it was cut in half usually lengthwise anteroposteriorly and the cut surface of one or both halves was photographed. Tumors to be corroded were then placed in commercial hydrochloric acid in the incubator until digested. Specimens to be cleared were further sliced into thin slices not quite completing the cuts and started through the dehydrating alcohols.

## The Blood Vessels of the Normal Uterus

The arteries of the normal uterus follow a fairly constant and definite pattern (Figs. 1 and 2). The course of the uterine artery along each side of the uterus and its free anastomosis with the ovarian artery on the same side is well known. It is also well known that one uterine artery anastomoses freely with the other. It is interesting in these specimens that the ovarian artery usually comes off about halfway up unless distorted by the presence of a myoma. From the uteroovarian anastomosis a large branch of the uterine artery usually goes on over the fundus. The fundal branch however is not always an exact continuation of the uterine (Fig. 1). From each uterine artery low down numerous cervical branches course downward but in surgical specimens they are lost by stripping off during operation. From the level of the internal os each uterine artery gives rise to short branches which arch around and penetrate the front or back of the uterus and to these the term "arcuate" has been given. They lie between the outer and middle third of the uterine wall either front or back. They branch at once into many branches which course over the outside of the uterus, and anastomose freely with similar branches from the opposite uterine artery. It is through this peripheral anastomosis that free communication from one artery to the other takes place. From the arcuate arteries, also, and all pointing toward the uterine cavity, the tortuous radial arteries arise. These branch near their bases but terminally end up toward the endometrium (Fig. 2).

In corrosion specimens there is always a small arteriolar tuft on the end of each radial artery which points toward the endometrium. These vessels are at present not considered to be the spiral arterioles of the endometrium itself, because it is uncertain that the injection mass enters them regularly. They are not visible in cleared specimens.

The uterine veins apparently contain no valves and may be easily injected. As said before the venous supply of the uterus is rich. The uterus during injection turns completely black from the pigment in the neoprene and the process of venous injection reminds one of filling a hot water bottle. A rich plexus in the endometrium, which usually fills, is fed by the terminal branches of the radial arteries and communicates with the large and rich plexus in the myometrium. There is a zone of myometrium about the uterine cavity which is relatively anemic venously and appears on the cut surface of all gross specimens (Figs. 8 and 11). About the periphery of the myometrium there are collecting veins, usually accompanying the arcuate arteries, which convey the venous blood of the uterus to the uterine veins overlying the uterine arteries in the broad ligament.

It is needless to say that aside from the variations in the uterine blood vessels produced by myomas they naturally vary with the age of the patient and with the phase of the menstrual cycle. This is especially true of the veins. It is the rule in the woman who is near a menstrual period, or bleeding, to find the endometrium well injected venously and the injection mass even in the uterine cavity (Fig. 8).

## The Blood Vessels of Myomas

In corrosion specimens the direct observation of the blood vessels of the uterus and its contained myomas is easy. The black venous injection mass is so heavy that the general contour of the specimen is retained

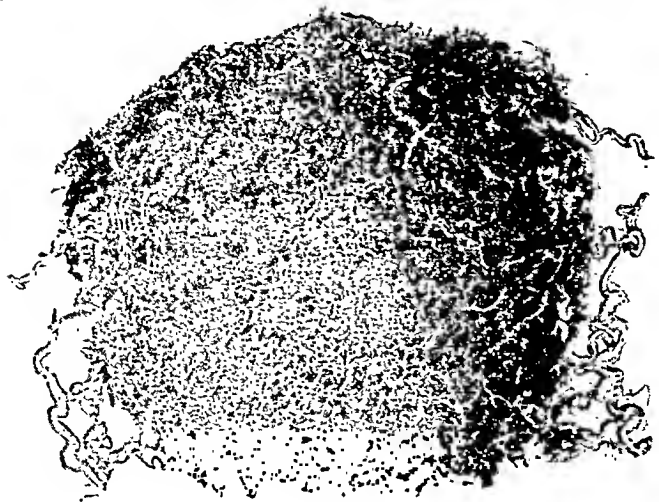


Fig. 1.—Corrosion cast of uterus showing black venous mass and uterine arteries with arcuate branches. Uterine veins cut away. Fundal branch toward top on either side.

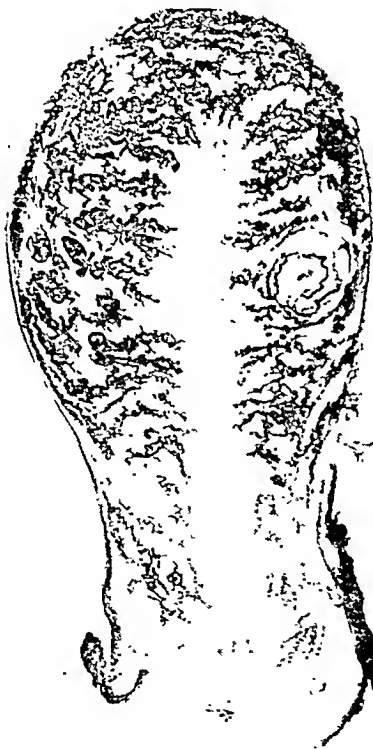


Fig. 2.—Arterial pattern of uterus. Spalteholz cleared preparation. One small myoma in uterine wall. Cervix does not inject in a surgical specimen.

and from this elastic sponge the red arteries may be dissected out if desired. The actual myoma is usually a mass of branching arteries containing few or no veins. The veins are usually concentrated about the periphery of the tumor, and enter it only a short distance or not at all. The arterial mass of vessels may be rolled out of its bed in the corrosion preparation and remain attached to the uterus only by its feeding radicals.



Fig. 3.—Specimen ready to inject. Long cannulas are in uterine veins. Small mass under myoma is an ovary.

From the injections of many different tumors it is obvious, as is well known, that myomas vary greatly in vascularity. In some the mass of arteries will be almost as large as the tumor itself, in others the cast will be much smaller. Holmgren's idea that white compact myomas have fewer vessels is not borne out in this study. As far as the degree of arterial proliferation is concerned no definite rules can be made but, there is the impression that some pink myomas especially those of coarser texture are apt to contain a few veins and show less arterial proliferation. This is logical in that less arterial proliferation is necessary to reach the venous circulation. Larger tumors seem more vascular but probably have no more vessels actually, the mass being larger because of proliferation necessary to keep pace with growth of the tumor.

In any myoma the arteries are coarse as they enter the tumor and branch over its surface. When an individual vessel in a myoma is teased out it is found to be very arborescent, some branches entering the substance of the tumor for quite a distance and others not so far. There

are branches connecting with other vessels approaching from other portions of the tumor. Each branched artery at the end of its finer radicals in the substance of the myoma presents a fine tuft of vessels similar to those at the end of the radial arteries in the uterus. Under the microscope these tufts seem to be arterioles. As separate vessels they are not visible to the naked eye in the corrosion specimen and certainly do not appear in x-ray plates or in the Spalteholz cleared specimen. The presence of these tufts suggests that there is a capillary bed in the myoma which, from the position of the veins, must drain toward the periphery of the tumor to empty into the venous system. Therefore, from study of corrosion specimens it would seem that ordinary arteriovenous exchange in a myoma is through the medium of a capillary bed. No evidence from dissection of the casts was ever found that the same artery could carry blood in and out of a myoma. There is also no evidence at present that injection fills lymphatics.



Fig. 4.—Corrosion cast of specimen in Fig. 3. Venous mass dissected away to show large tortuous arteries of right uteroovarian anastomosis with arc over fundus to left ovarian artery. Left uterine artery very small. Myoma is a mass of proliferated arteries. Most of veins over the myoma have been removed.

Although the uterus is a mass of veins and is almost correctly spoken of as the "venous heart" of the pelvis very few veins as a rule penetrate very far into the myoma itself. Myomas of coarse texture or, as stated above some pink myomas, occasionally show a scant venous injection of their substance. There is every evidence to indicate that the failure to inject the veins in a myoma is not the fault of the medium or method.





Fig. 5.—Veins over the surface of a pedunculated myoma forcibly injected. Spalteholz cleared specimen. No veins penetrated the tumor more than 2 cm. Solid black injection below is a portion of the uterus.



Fig. 6.—Spalteholz cleared specimen. Large myoma to left 9 cm. in length had only one nutrient artery. Degeneration. Other smaller myomas in uterus had better blood supply.

Every device was employed to force the venous injection mass into any veins that might be in the substance of the tumor. In one instance (Fig. 5), the pedicle of a pedunculated myoma and the veins over its surface were thoroughly "milked" and still no venous material went very far below the surface. There is certainly never a venous supply in a myoma approaching the richness of that in the myometrium.

As is well known, the arteries and veins of the uterus containing fibroids are frequently much increased in size, especially in larger tumors. One is struck with the fact that in a uterus containing many myomas there may be a division of labor, so to speak, between the uter-



Fig. 7.—Arteries around a submucous myoma under endometrium. Spalteholz cleared specimen. This myoma received branches at opposite poles from each uterine artery.

ine vessels, one artery feeding some of the tumors, the other uterine running to the others (Figs. 8, 9 and 10). In the case of many intramural tumors of good size there are branches to the tumor from a vascular arc in the uterus contributed to by one uterine and both ovarian vessels. The other uterine vessel may be very small by comparison (Fig. 4). Anastomotic branches from one side of the uterus to the other may become quite large and conspicuous.

Intramural myomas of any size are very rarely found without three or four nutrient vessels entering its substance. The vessels are all branches of a vascular arc in the uterus and usually enter the tumor at opposite poles. It is quite clear that any myoma of larger size which has only one nutrient vessel is to be considered undernourished and may al-

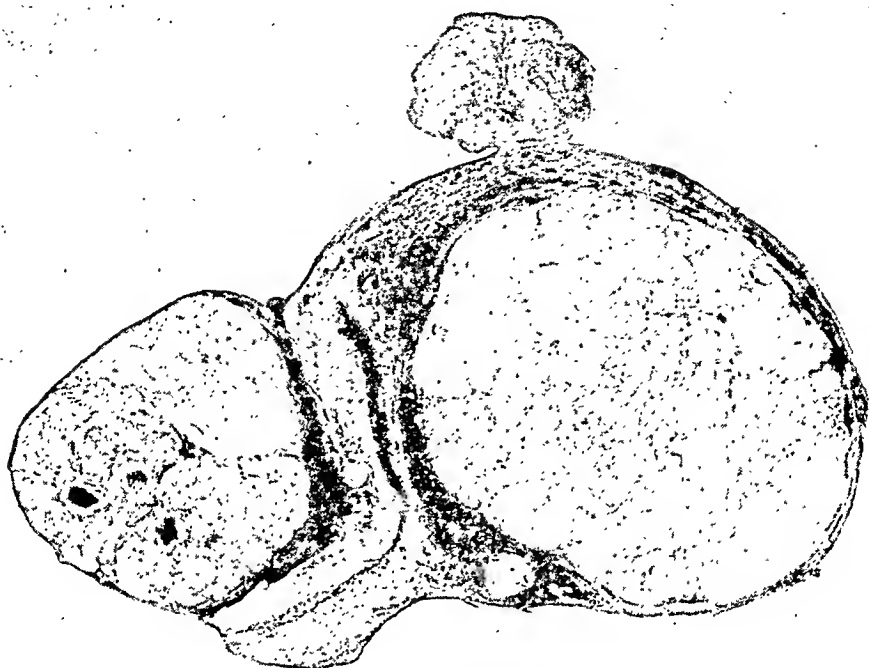


Fig. 8.—Myomas in uterus removed during menstruation. Largest myoma 8 cm. in diameter. Black venous mass in uterine cavity. Occasional veins injected in larger tumor with mass of proliferated arteries smaller than normal. Tumor to left is compound myoma with veins between nodules, two of which show small areas of degeneration.

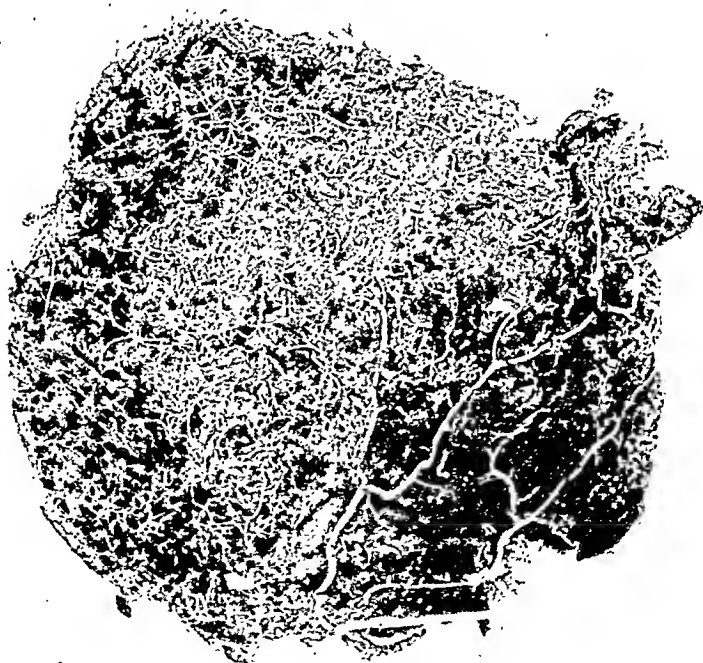


Fig. 9.—Posterior view of specimen in Fig. 8. Veins partly removed. No branches to large tumor. Large ones to smaller compound myoma (bottom of picture). Pedunculated tumor split open to show internal arterial mass proliferated from two feeder arteries.

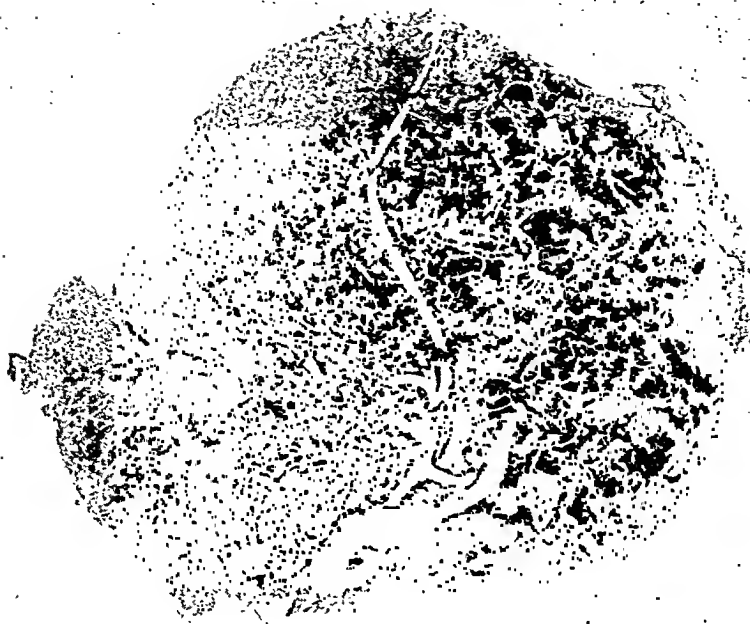


Fig. 10.—Outside of other half of specimen in Fig. 8. Shows the veins to the large tumor. Uterine cavity split open at left.

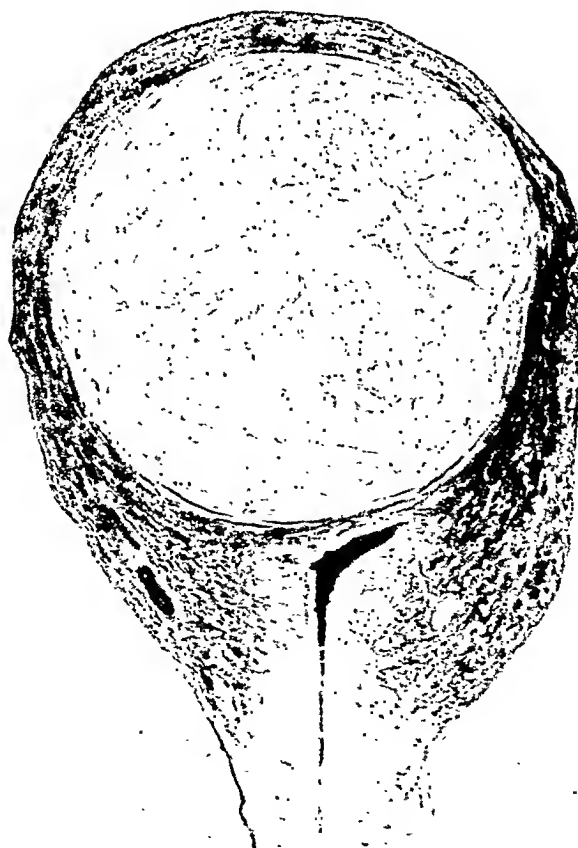


Fig. 11.—Compact intramural myoma. No veins could be injected in this tumor.

ready show signs of degeneration (Fig. 6). In very small myomas it may be difficult to tell whether there are multiple nutrient vessels or not. Frequently the substance of the tumor seems to be fed by the arborescent proliferation of one small artery, but there is no reason why neighboring arteries in the myometrium might not be sending in small short branches. As stated above, it is very plain that this happens in larger tumors. (Figs. 11, 12, 13.)



Fig. 12.—Major arteries dissected from cast of entire specimen in Fig. 11. Near lower end of right uterine artery is the arterial mass of a small myoma.

It is probably true that the correct picture of the blood vessels of a myoma cannot be obtained from the study of pedunculated nodules. As the myoma is extruded from the uterus some of the branches feeding it may become of secondary importance and on occasion there may finally appear to be only one nutrient artery. Such a tumor degenerates unless it acquires collateral vessels from an adjacent structure such as omentum, etc. As a rule in subserous and pedunculated myomas that show no degeneration or parasitism, the pedicle or base is made up of many arterial branches from the aforesaid are in the uterus, the only change from the intramural position being that their polarity is disturbed: viz., the vessels now enter the capsule of the tumor all at one point. The same is true of well pedunculated submucous myomas, but in submucous myomas still fairly well embedded in the wall of the uterus, it has been observed that nutrient vessels still enter the tumor from the myometrium at opposite poles.

Similar to Sampson's observations no good venous injections have been obtained of the endometrium over the projecting surface of a submucous myoma. The arteries over the surface of the tumor are intact and under the endometrium in the capsule of the tumor (Fig. 7). Therefore, with relative anemia over a submucous myoma, it is evident that unless ulcerated, the uterine bleeding frequently accompanying such

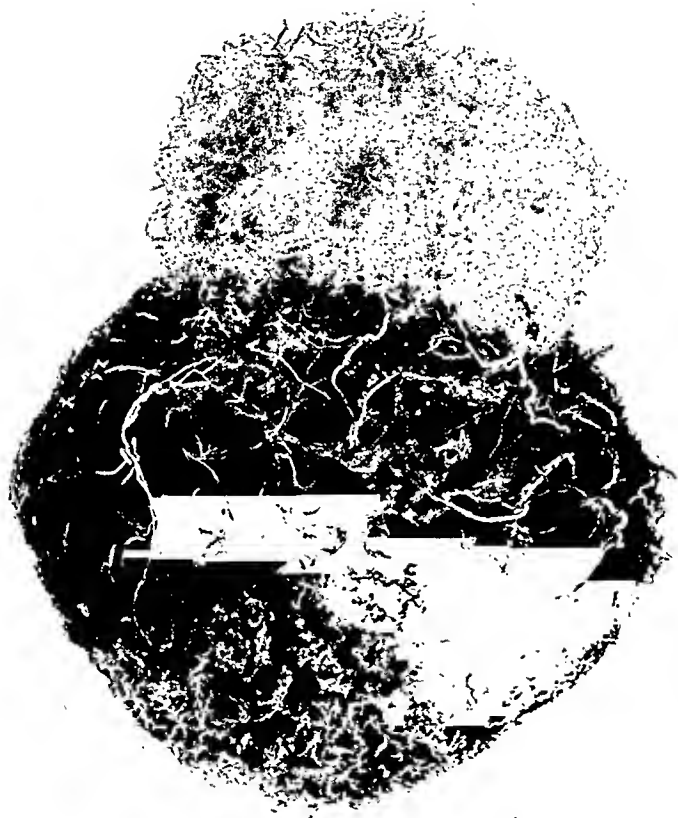


Fig. 13.—The blood vessels of the myomatous uterus. Corrosion cast of the half specimen of Fig. 11. Red arterial mass of myoma rolled up out of its bed showing the nutrient vessels. Radial arteries project toward uterine cavity below. This picture shows very well the nature of the corrosion preparation.



tumors does not come from the tumor itself, but is, when present, from the endometrium near-by which sometimes injects heavily with the venous mass. The endometrium may be normal or abnormal histologically but it seems logical to conclude that the bleeding may be contributed to by poor contracting power of the uterus due to the presence of the tumor.

Mention must be made of some myomas which on injection show admixture of arterial and venous injection masses. No absolute statement to cover all cases can be made as to the cause of this abnormality of injection but there is the impression that it is usually due to injury of the specimen during its removal. With the rich venous bed of the uterus and the large veins about the periphery of myomas, it is not surprising that the venous system might easily fill with any arterial mass set free anywhere within the specimen. This is what usually happened although occasionally the venous injection mass also seemed to flow back into the arteries. These specimens are rare and further study of them is being made to form some conclusion as to the presence or absence of actual arteriovenous fistulas in myomas. If free communications exist a revival of some of the older ideas about myoma heart might be in order. Four such specimens in the first sixty studied were encountered and injury was proved in both of two smaller ones. In two larger specimens injury was not found and the specimens were discarded.

### Summary

Employing anatomical methods which allow the direct inspection of the blood supply of the myomatous uterus, the distortions in the blood vessels of the uterus caused by these tumors and the intrinsic vessels of the tumors themselves were studied. The fact that most myomas are a mass of proliferating arteries and contain few or no veins within their substance is confirmed. No normal myoma has only one nutrient artery. The frequent arteriolar tufts seen in corrosion specimens are pointed out as evidence that a rich capillary bed probably exists, emptying toward the periphery of the tumor. No evidence of blood entering and leaving a myoma by arterial channels was found. Free arteriovenous anastomoses were encountered four times in sixty specimens but probably were tumors injured at operation. Even overinjection of arteries does not fill lymphatics in or around myomas.

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## FALLACIES IN SOFT TISSUE PLACENTOGRAPHY\*

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WHEN haemorrhage occurs from the uterus at or near term grave issues may depend on a rapid and accurate determination of the position of the placenta. The diagnosis is usually made by digital palpation, but in a major degree of placenta praevia this examination will sometimes provoke alarming bleeding. For this and other reasons alternative methods of investigation have been sought, and, in particular, much attention has been paid to the possibility of radiological diagnosis. Some success has been achieved by the use of methods that reveal the thickness of tissue separating the foetal head from the bladder wall; radio-opaque substances injected into the amniotic sac have also been used to display the outline of the uterine wall. These methods—especially the first—have a certain usefulness, but they do not concern the purpose of this paper, and will not now be further considered.

In 1934 Snow and Powell<sup>1</sup> claimed that the soft tissues of the pregnant abdomen, including the placenta, could be visualised by "straight" radiography. Further contributions appeared in 1939 by Snow,<sup>2</sup> and by Snow and Rosensohn.<sup>3</sup> In 1940, Dippel and Brown<sup>4-6</sup> reported favourably on the simplicity and reliability of the method, claiming successful identification of the placental site from a single radiograph in 90 per cent of cases. Following these leads, soft-tissue placentography has been put to considerable test in the Nuffield Department of Obstetrics and Gynaecology at Oxford. At first a favourable impression was formed, but with increasing experience it was found that the interpretation of the x-ray films was open to serious error. The conclusion has now been reached that, in the form originally described, the method may lead to grave mistakes in diagnosis.

### Method

In a good radiograph it is usually possible to trace the outline of the wall of the pregnant uterus for a considerable part of its circumference. In the usual anteroposterior picture much of the view is obscured by the maternal skeleton, and for that reason the lateral or profile view is of greater service. In such a radiograph the following structures can be seen: (1) the maternal skin, (2) the muscles of the abdominal wall, (3) the wall of the uterus, (4) the surface of the foetus and (5) the deeper structures of the foetus.

\*Contributions from foreign sources are not accepted as a general rule for publication in the JOURNAL. However, this particular article bears a close relation to similar research in this country and the appended rebuttal is made by an American author. The English spelling has been retained.—Editor.

There is an extreme range of density in the radiograph between the heavily exposed anterior portion, and underexposed posterior portion. If, however, the picture is viewed by an illuminant that can be varied from dimness to extreme brilliance, much of the difficulty caused by uneven density is overcome. It is also a considerable advantage to reduce the time of development of the films to one-third of normal. Experiments have been made with various forms of differential filters to secure an even film exposure. Although improved results have been obtained, I agree with Dippel that the advantages of such devices scarcely compensate for the troubles encountered in their use. In a stout subject it is best to make two pictures: the first is taken with a low voltage to reveal the anterior structures; the second, taken with a much higher voltage, displays the thick posterior structures. During the second exposure the anterior area should be shielded by a lead sheet placed between the patient and the x-ray tube.

In radiographs so obtained, the uterine profile is clearly seen. Immediately above the pubes the uterine wall is usually sharp in outline and even in thickness. At a higher level a sudden change takes place. While the outer surface continues in even outline, the inner surface abruptly alters, so that the thickness of the uterine wall now appears to be twice, or many times, as great as before; in addition, the outline is usually less sharply defined. Tracing the shadow still further, the wall is again seen to diminish so that it resumes—or nearly resumes—its original thickness. The expansion commonly extends over a quarter or a third of the visible portion of the uterine wall; it oftenest occurs anteriorly, or in the fundus; it rarely occurs in the posterior part of the body. (Figs. 1 and 2.) This thickening is accepted by Snow, Dippel, and their associates to represent the placenta. It is not possible to distinguish placenta from the uterine wall, for, except in rare instances of placental calcification, the radio-opacity of these organs is so similar that the shadows usually merge into one. Dippel puts the matter thus: "*The placenta is localised in the region where the structures between the outer uterine wall and the foetal soft parts are definitely increased in thickness.*"

### Present Investigations

Using the described methods, a representative series of radiographs was obtained from normal patients in the last 8 weeks of pregnancy. In almost every case a localised thickening of the uterine wall could be seen clearly. A critical analysis was then made of some 30 films selected because of technical superiority. As a result of this study, many questions pressed for answer: among them were the following. Why should the placenta be so conveniently placed that its outline could be clearly seen in almost every lateral view? Why should the placenta be oftenest seen over the ventral surface of the foetus? (Snow and Powell state: "In practically all cases the ventral part of the foetus faces it.") Why should the placenta be difficult to visualize in cases of hydramnios? Why should the foetal limbs sometimes make such a deep indentation in the placenta? There seemed to be one common answer to all these puzzling questions. The thickening of the shadow of the uterine wall might represent not only the placenta, but also a localised excess of amniotic fluid.

Now, there is no reason to suppose that the foetus, surrounded by fluid, must necessarily remain poised in mid-cavity; it is far more probable that it usually rests with one surface applied to the uterine wall while the other is separated from it by a layer of amniotic fluid varying in depth in different cases.



Fig. 1.—Lateral view of pregnant abdomen. The lower three arrows point to skin, abdominal-wall muscles, and outer surface of uterus respectively. The other indicate the local thickening of the uterine wall.

It was a basic assumption by Snow and Powell that in this method of placentography that the placenta and the liquor amnii cast shadows of different density. These writers state: "... the placenta consisting of tissues and blood causes a greater obstruction to the roentgen rays

than the amniotic fluid which is of low specific gravity. Hence the latter casts a blacker shadow." Yet, paradoxically, Snow elsewhere states that the placenta cannot be revealed in cases of hydramnios: "the large quantity of fluid casts a shadow which cannot always be differentiated from that of the placenta."<sup>2</sup> If, then, the placenta cannot be outlined

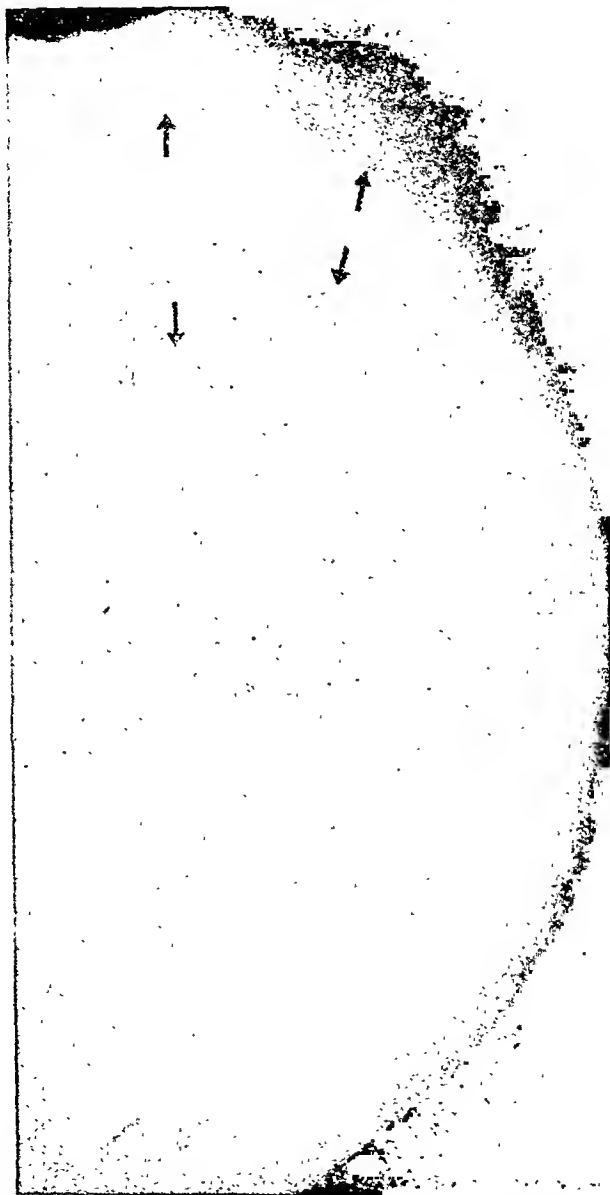


Fig. 2.—Lateral view of pregnant abdomen. Arrows indicate the local thickening of the uterine wall, situated in this case over the posterior part of the fundus.

against amniotic fluid when that is present in excess, by what new token can it be displayed against a background of the same fluid present in normal quantity? It seemed more probable that the uterine wall, the placenta and the amniotic fluid all cast shadows of similar density, and that the localised "bulgings" of the outline were often caused by

“pools” of normal amniotic fluid rather than by placental tissue. Various experiments were devised to put this supposition to the test, and these will now be described under six headings.

1. *Can Placenta Be Distinguished From Amniotic Fluid?*—Snow and Powell believed that in normal cases the amniotic fluid and placenta cast shadows of different density. It is far from clear that this assumption was ever justified, nor does it seem that their statement has since been critically examined. A simple experiment was devised to put the matter to test.



Fig. 3.—Lateral radiograph of a placenta suspended by its membranes from a wire loop 7" in diameter; the foetal surface is uppermost. The inner surface of the placenta can be easily seen; two small pieces of lead have been placed on the surface to make its identification certain.

A normal, fresh placenta, foetal surface uppermost, was attached by its membranes to a wire loop 7 inches in diameter. The organ thus assumed the shape it previously held in utero. A lateral radiogram was obtained, and, as was to be expected, the inner surface of the suspended placenta was clearly outlined (Fig. 3). A quantity of normal liquor amnii (obtained by catheter puncture) was now carefully poured into the saucer-shaped placenta, and a second radiograph obtained. The appearances were now completely changed: all trace of the inner placental surface had disappeared (Fig. 4). This experiment was repeated using three different placentas, with like results. Thus, even under the ideal circumstance of examining the isolated placenta, the radio-opacity of tissue and fluid proved to be too nearly alike to allow of any differentiation.

Regarding placenta and uterine wall, all workers agree that soft-tissue roentgenography of the pregnant abdomen will not enable one to be outlined against the other unless in the rare instance of a partly calcified placenta. The experiment now described enables the firm statement to be made that the uterine wall, the placenta and the amniotic fluid are all three so nearly alike in opacity that it is impossible to differentiate one from another by any usual method of radiological examination.

2. *The Nature of the Dark Band Surrounding the Foetus.*—In most radiographs of a full-time pregnant uterus the foetus is seen to be surrounded, for the most part, by a well-marked, dark band that varies in thickness up to about 75 mm. This dark, or relatively transparent, space appears to separate the foetus from the uterine wall, and at first sight

it is natural to regard it as the shadow of a layer of amniotic fluid; this assumption can lead to erroneous interpretation of radiographs of the pregnant abdomen.

The nature of the dark band has been the subject of considerable speculation; it has been attributed to the presence of a layer of vernix caeseosa, and even to a deceptive photographic effect. In 1939 Weintraub and Snow investigated this matter. They immersed a foetus in salt solution of a density equal to that of amniotic fluid and found that the foetal skin and subcutaneous tissue were considerably more transparent to the roentgen rays than the surrounding fluid or the underlying foetal muscle. The appearances seen in radiographs of the pregnant uterus were thus explained.



Fig. 4.—The same placenta after it had been partly filled with amniotic fluid. The inner surface has now completely disappeared although its position is indicated by the two pieces of lead.

As this interpretation was of fundamental importance concerning the matter in hand, it was decided to repeat Snow and Weintraub's experiment and to make it more realistic by using actual liquor amnii. Accordingly, the fluid obtained when the foetal membranes were punctured by catheter to induce labour, was used to fill a paraffin-waxed cardboard box. A full-time stillborn foetus was immersed in the fluid, and the radiograph shown on Fig. 5 was obtained. It will be seen that a dark band occupies the space between the muscle-tissues on the one hand, and the skin surface and the beginning of the amniotic fluid on the other. In other words, the subcutaneous tissue is considerably more transparent than either foetal muscle or amniotic fluid. A thin layer of foetal skin appears to equal, or even exceed, the opacity of the amniotic fluid. This experiment confirms, in the main, the previous finding by Weintraub and Snow that the dark band, so notable in many radiographs, is of foetal origin. *It does not represent a layer of amniotic fluid.*

In radiographs of the pregnant abdomen, the dark layer can be identified with certainty. It is found to be thickest in those regions where the foetal fat is best developed—over limbs and buttocks—but it is scarcely visible where fat is absent, as, for example, over the skull. It is much in evidence when the foetus is large, but is only seen with difficulty when the foetus is premature. The *outer* margin of the dark band marks the foetal skin, and may mark the beginning of the uterine wall or placenta:

but, as has been shown, it may equally well mark the beginning of a layer of amniotic fluid. It is often impossible to decide between these three possibilities.

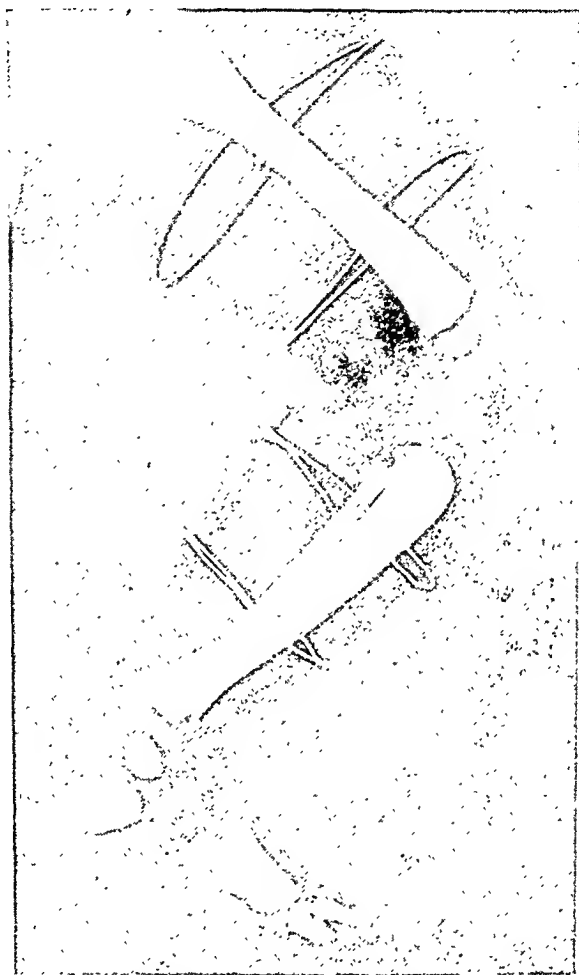


Fig. 5.—Limb of a foetus radiographed while completely immersed in liquor amnii. Lead wires twisted around leg indicate position of skin surface. The dark band surrounding the limb is caused by the relative transparency of the subcutaneous tissues. A thin layer of skin approximates—or very slightly exceeds—the opacity of the amniotic fluid.

3. *The Thickness of the Placenta.*—The radiographs published by Snow, Dippel and their co-workers, show that the space described as placental shadow is, in some cases, surprisingly thick. No measure is included in the pictures, but by indirect methods a fairly accurate estimate of the thickness can be made. Thus, in some of the lateral views, the maternal lumbar vertebrae are clearly seen. If one assumes that the anterior surface of the 5th lumbar vertebra measures, from above downward, approximately 3.2 cm., this span can be used to judge the distance between the outer wall of the uterus and the inner surface of the shadow stated to be placenta.

Snow and Powell's reproductions are made from direct tracings of full-sized radiographs. Six of these were carefully examined. The thickness of placenta plus uterine wall was estimated to be 3.4, 4.0, 4.8, 4.8, 6.5, and 7.2 cm. respectively. Two of Snow and Rosensohn's repro-

ductions of radiographs were similarly examined. The measurement was 6.2, and 5.6 cm. respectively. In one of Dippel and Brown's radiographs the measurement was 8.3 cm. If from these figures is subtracted the normal thickness of the uterine wall (stated by Snow to be 1.5 cm., and by Dippel and Brown to be 1.24 cm. in the magnified radiographic shadow), it will be seen that the thickness of the placenta was never less than 2.5 cm. and in one case was more than 5.7 cm.

To determine the usual placental thickness, twenty-five unselected placentas were collected and laid on a stone slab; the organ was trans-fixed with a needle and the thickness marked on the shaft. The measurements were as follows: 2 cm. or under, 4 cases; 2.1 to 2.5 cm., 9 cases; 2.6 to 3 cm. 11 cases; 3.1 cm. one case.

These measurements refer to the expelled, semi-retracted placenta. The true thickness of the organ when fresh and attached to the uterine wall may be less. In three cases I have been able to get measurements of the placental thickness from uteri that have been fixed with contents in situ. In one case (a seven-months' gestation) it measured 2.9 cm. There was, however, a considerable formation of gas in the tissues, and this measurement may therefore be misleadingly great. The two other cases were of full-time gestations: in one the placenta was less than 1.5 cm., in the other it was less than 2 cm. In Barbour's *Anatomy of Labour* the majority of drawings (based on post-mortem specimens) show a placenta below 2 cm. in thickness; in two cases the thickness appears to be between 2.5 and 3 cm., and in one case it is (very vaguely) about 3.4 cm.

Assuming that the placenta rarely exceeds 3 cm. in thickness, it will be realised that nearly all the illustrations published in support of soft-tissue placentography reveal a "placenta" of great size, the thickness in one case amounting to nearly twice the maximum probable measurement. There is thus strong presumptive evidence that the shadows under consideration were produced partly, or wholly, by amniotic fluid.

As already stated, it is significant to find that Snow realizes this possibility of error. He writes:<sup>3</sup>

"If hydramnios is present its shadow runs together with that of the placenta. It then appears as if the placenta were completely surrounding the foetus. Since this is extremely unlikely, the diagnosis of hydramnios is made."

Thus, in the original description of soft-tissue placentography, a fallacy is admitted, although its full significance does not seem to have been appreciated. It is not unfair to paraphrase Snow's words thus: *If the shadow in question resembles a placenta in shape, the organ has been identified: If, however, it does not agree with one's preconceived idea of placental shape and thickness, then this otherwise identical shadow must represent amniotic fluid.* It is difficult to accept such reasoning; if a "large" shadow is caused by fluid, why should a smaller shadow not be caused by the same fluid in smaller amount? In a previous section it has been shown that amniotic fluid and placenta do, in point of fact, cast shadows indistinguishable in density. It is thus evident that the diagnosis rests essentially on a similarity to the supposed shape of a placenta in utero, and on this basis there can seldom be any warrant of certainty.

In fairness it must be added that in many instances the shadows in question *may* represent placenta. With experience, one's interpretation of radiographs will also become more reliable. Nevertheless, the defini-



tion of placental shadows as given in the earlier descriptions of this method of radiology is seriously misleading, and re-definition is urgently required.

4. *The Indentations on the "Placental" Surface.*—Snow and Rosensohn mention a frequent indenting of the placenta by the foetal limbs; these irregularities they term "digitations," and they believe that they are caused by uneven pressure on the soft placental tissue. In the present investigation, many examples of such indentations were encountered; often they were surprisingly deep (Fig. 6). In Snow's own



Fig. 6.—Indenting of "placental" shadow by the hand and the shoulder of the foetus.

pictures the placenta is reduced to a half or even a quarter of its thickness by these pressure marks—a fact surprising to anyone familiar with the normal texture of placental tissue. The irregularities might be caused by the rays striking the abdomen at such an angle as to show overlapping of shadows: this possibility is considered by Snow but dismissed as an incomplete explanation. If, however, the proposition is accepted that the shadow in question is caused by amniotic fluid, then the irregularities of that shadow are readily understood.

It is not denied that the placental surface may sometimes be slightly indented by projecting foetal limbs—this is especially likely when there is less than the usual quantity of amniotic fluid. But the sharp and

deep indentations so often seen in the substance surrounding the foetus are, almost certainly, of a different nature. They are the natural consequence of radiographing foetal parts against a fluid background.

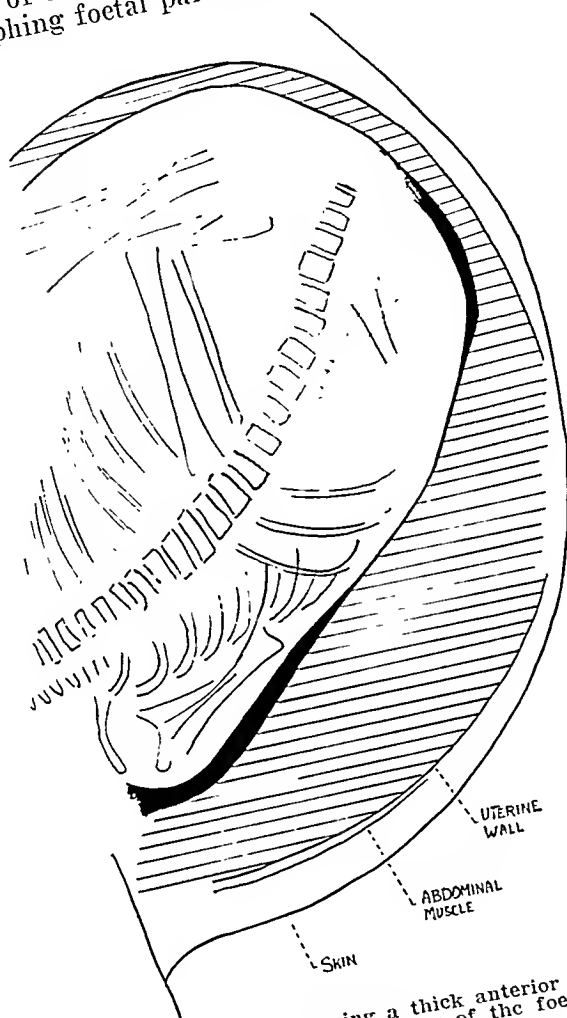


Fig. 7.—Tracing of radiograph showing a thick anterior "placental" shadow. The dark band caused by the relative transparency of the foetal subcutaneous tissue is also indicated.

**5. Effect of External Pressure.**—The thickening of the uterine-wall shadow is frequently confined to the anterior surface. If, as has been postulated, this thickening is, in most instances, due to a local excess of amniotic fluid, it should usually be possible to alter the appearance by applying external pressure. Experiments have confirmed this expectation.

Patients were selected who showed anteriorly situated thickenings of the uterine shadow, corresponding to the original description of placental site. Examination was made with the women standing in the erect position. After the first exposure a sheet of firm cardboard was used to indent the abdominal wall where the uterine shadow was broadest. In the example illustrated (Figs. 7 and 8) it will be seen that the pressure has had the effect of reducing the thickness of the shadow to nearly a third of its previous dimension. Bearing in mind that the uterine wall itself is approximately 1.25 cm. in thickness, it will be

realised that the "placenta" has been reduced to a still smaller fraction of its previous thickness. Such a change as this is incomprehensible except on the basis that it represents a displacement of amniotic fluid.

6. *Displacement of Amniotic Fluid by Air.*—Continuing these experiments, another method of displacing the amniotic fluid was put to test. A small quantity of air was introduced into the amniotic sac, and radiographs were then obtained with the patient positioned to show the air-bubble in relation to the supposed placental tissue.

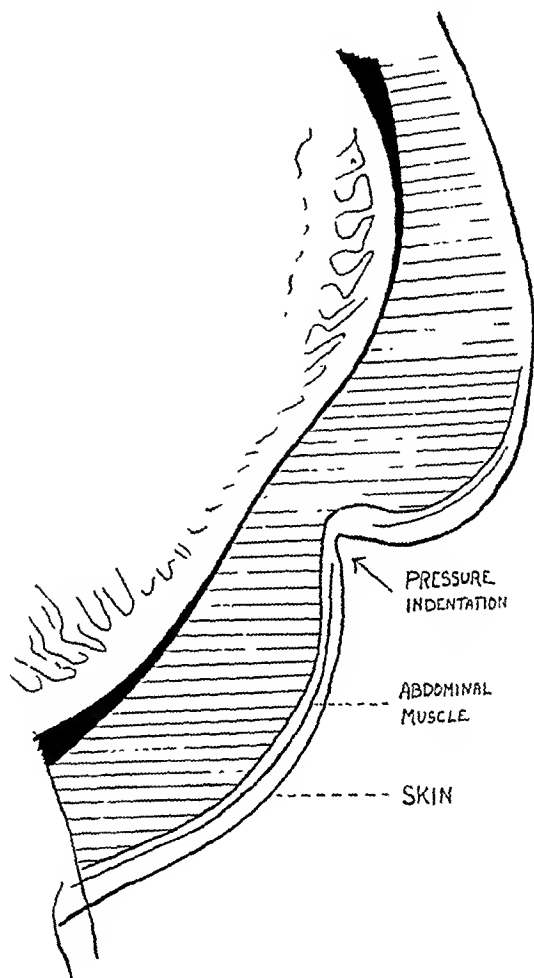


Fig. 8.—From same patient as Fig. 7, showing effect of external pressure on the supposed placental shadow.

The patients selected were due to have labour induced by perforation of the foetal membranes. With the usual technique, a Drew-Smythe catheter was introduced, and the amniotic sac punctured above the presenting part. After several ounces of fluid had freely escaped, air was carefully injected to the amount of about 100 c.e. Examination was then made with the patient first in the erect, then in the horizontal position.

In the example shown (Figs. 9 and 10) the patient appeared to have an anteriorly situated placenta according to the original definition; after the air injection this localised thickening completely disappeared and the

uterine wall was revealed in its true thickness. All suggestion of placenta had vanished! A similar result was obtained in a case in which the foetus presented by the vertex, and in which the "placental" thickening was situated between the anterior wall of the uterus and the thorax of the foetus.

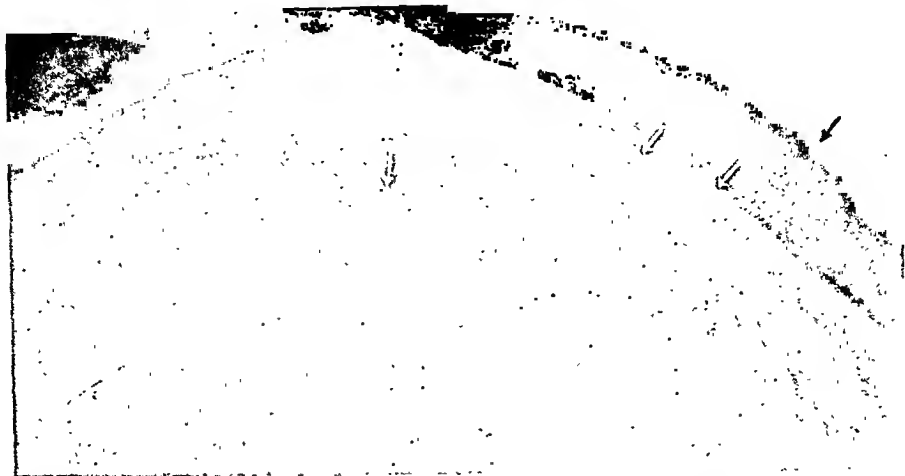


Fig. 9.—Anteriorly situated "placental" shadow from a case in which the foetus presented by the breech. The arrows on the right indicate skin, abdominal-wall muscles and outer uterine surface respectively. Arrows on left indicate extent of the "placental" bulge.

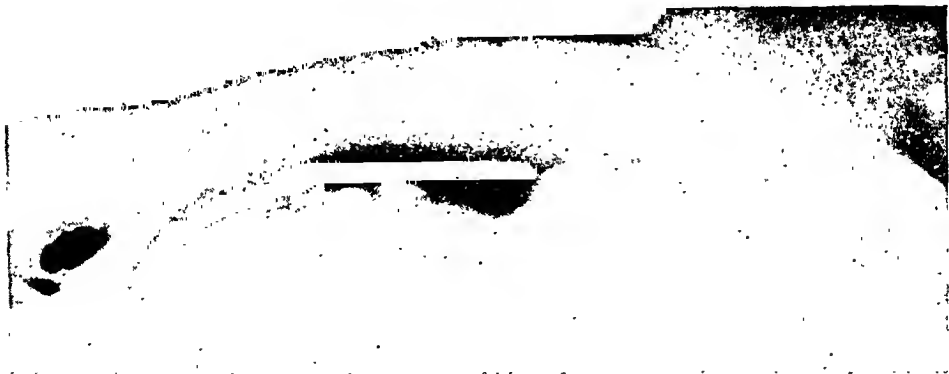


Fig. 10.—Radiograph of same case as Fig. 9, after air had been introduced into the amniotic sac. The bulge has now quite disappeared and the uterus is seen to be normal in thickness at the site of the supposed placenta.

This last test finally disposed of any doubt regarding the nature of the localised thickening of the uterine shadow in the cases investigated. The shadow has proved to be partly, and much oftener, wholly, the result of an uneven positioning of the foetus in the uterine cavity with consequent uneven distribution of surrounding fluid. It is impossible in any ordinary radiograph to distinguish between placental tissue and a local excess of amniotic fluid.

### Conclusions

1. Serious errors of interpretation are likely to occur in the use of the soft-tissue method of placentography as originally described.

2. Experiments show that the dark band surrounding the foetus in utero is the result of the relative transparency of the subcutaneous tissue of the foetus. It does not represent amniotic fluid: the conclusions of Weintraub and Snow are in the main confirmed.

3. Experiments are described which prove that the uterine wall, the placenta, and the amniotic fluid are all similar in radio-opacity. A local collection of amniotic fluid (caused by an uneven position of the foetus in utero) gives a shadow indistinguishable on ordinary examination from placental tissue. The shape of the shadow may give a clue to its identity but certainty in diagnosis is seldom possible on this basis alone.

4. Critical examination of previous work raises doubt regarding the accuracy of the interpretation of the experimental findings. In some of the radiographs the thickness of the "placenta" considerably exceeds the thickness of the normal organ.

5. The deep indentations frequently seen on the "placental" surface can be readily explained on the basis of the fluid nature of the shadow-producing substance.

6. In test cases, the localised thickening of the uterine-wall shadow (the placental site according to the original definitions) disappeared when external pressure was applied.

7. In test cases, air introduced into the amniotic sac revealed a uterine wall of normal thickness at the site of the supposed placenta.

8. Positive findings from this method of placentography should be accepted with reserve: negative findings may have a limited field of usefulness.

*Postscript.*—Since this paper has been in preparation two further publications on soft-tissue placentography have appeared. Lloyd and Samuel<sup>9</sup> use a tomographic technique: in a short series of cases their results seem to be similar to those of previous workers. Buxton, Hunt and Potter<sup>10</sup> claim successful identification of the placenta in 86.1 per cent of 108 cases: when in doubt they resort to the older method of cystography. Nothing in these more recent publications calls for modification of the opinions already expressed.

*Acknowledgements.*—I am indebted to Dr. A. E. Barelay for helpful criticism in the preparation of this paper; my thanks are also due to my technician, Mr. A. Scott, who has assisted in the experimental work.

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### Comment

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Our experience with this method does not coincide with that reported by Moir in that the method gave a favorable impression from the outset and has continued to do so. Moreover, the number of roentgenograms considered unsatisfactory for purposes of interpretation has decreased with experience. Likewise, confusing shadows have been clarified. Notable among these has been what we have called the "nuchal" shadow and which is shown in Moir's Figs. 6 and 9. In the early days of our work, Brown and I recognized that these were not shadows of the placenta. They could not have been because the placental shadow was definitely localized elsewhere on the wall of the uterine cavity. We thought at first that this (Fig. 6) represented a thickened portion of the uterine wall marking the division between the upper and lower uterine segments. However, when we began seeing similar shadows well up on the uterine wall in association with breech positions (Fig. 9) we realized the error of our original interpretation and thereafter ignored such shadows except as collections of amniotic fluid between the uterine wall and skin of the fetal neck. Very little experience should be necessary in recognizing that these shadows could not possibly represent placental areas for they are too atypical in appearance and do not coincide with our knowledge of the size and shape of the placenta viewed in profile. One would avoid the possible errors in Figs. 6 and 9 by visualizing the whole of the uterine wall and not focusing attention on localized atypical areas of apparent thickening of the wall. We do not consider a roentgenogram adequate for purposes of visualization of the placenta unless the whole of the uterine wall above the bony pelvis can be made out.

Mention must also be made of Moir's error in explaining why lateral views are used and anteroposteriors are valueless. This is not because gestational shadows may be obscured by the relatively denser maternal shadows in the anteroposterior view but because the placenta is almost always implanted primarily over the relatively flat anterior or posterior uterine wall and rarely extends over the dividing lines between these. This has been well demonstrated by Torpin's method of amniotic sac distension, and we have made reference to this in our previous articles. Such being the case one would have to look at a lateral view in order to see the placenta in profile. We have never visualized the placenta except in a lateral view and no longer resort to anteroposterior views in attempting to visualize the placenta by soft-tissue roentgenography.

As for distribution of placental sites on the various areas of the uterine wall, we do not agree with Moir's experience. We have not observed any predilection for the anterior wall of the corpus uteri. In our last report in which the placenta was clearly visualized in 236 patients, there were almost exactly as many placentas implanted on the posterior as on the anterior wall of the corpus. In the smaller number implanted over the lower uterine segment, 26 cases, we observed a greater incidence of anterior implantations, a ratio to posterior implantations amounting to 8:1.

Moir's experiments constitute the major contribution of this paper but cannot all be accepted as final proof. While we have never doubted the indistinguishable nature of the placental and amniotic fluid shadows in the majority of roentgenograms, one cannot accept, as conclusive proof, his x-ray demonstrations of the delivered placenta. The undelivered and functioning placenta is not roentgeno-

graphically the same organ as the delivered placenta, which contains less blood. That the dark line separating the term fetus from its surrounding structures is due to subcutaneous fetal fat has long been accepted. It conforms too well to the fetal outline to be associated with anything but the fetal skin. Weintraub and Snow settled this argument in 1939. Furthermore, in unpublished works on vernix caseosa, Brown demonstrated that this waxy material cast a radiographic shadow different from the one surrounding the fetus.

The demonstration of the possible dual nature of a "placental" shadow is very clearly shown in the sketches of Figs. 7 and 8. It must be emphasized, however, that the applied pressure did not disprove the presence of placenta beneath the anterior uterine wall. Actually, it proved its presence there in conjunction with some amniotic fluid. Had this shadow been made up entirely of amniotic fluid, he should have been able to displace it completely by external pressure.

From what has already been said of localized atypical apparent thickenings of the uterine wall such as the "nuchal" shadow shown in Fig. 9, our group would never have made the mistaken diagnosis even without injection of air, but the experiment is a beautiful demonstration with conclusive proof. Moir appears to be unduly upset about our American way of calling a placental shadow a placenta simply because it fits our knowledge of the appearance of a placenta. We can see no reason why only a radiographic shadow which fits our preconceived idea of size and shape of the placenta should not be called a true placental shadow, whereas, if it does not meet these requirements it should not be called something else, such as excessive amniotic fluid. Quite aside from the logic of such reasoning, it must be admitted that no errors have been produced in soft-tissue localization of the placenta when strict criteria of that nature have been adhered to. Thus, at the time of our last analysis, the placental site had been checked in 22 per cent of the cases with acceptable films.

The fact that the radiodensities of uterine wall, placenta, and amniotic fluid are nearly the same in no way lessens the value of soft-tissue localization of the placenta. We have shown that in 90 per cent of lateral roentgenograms, it is possible to demonstrate uterine wall of normal thickness either anteriorly or posteriorly while the opposite wall appeared to be thickened. It was also pointed out that this area of apparent thickening fitted more or less our previously formulated ideas of size and shape of the placenta in profile. Whether the latter shadow is made up of placenta and amniotic fluid or placenta alone has not disturbed us for the fact has remained that the shadow either comprises or contains the placenta. The purpose of the special study is only to locate the placental site. In our experience, the size and shape of the shadow has supplied positive evidence of the location of the placenta, and, with normal appearance of the opposite uterine wall, has been the sole basis for localization. The experience of many clinics with hundreds of cases would seem to substantiate our views.

The reproduced roentgenograms of this paper are of high quality and strongly indicate that Moir's difficulties have been with interpretation and not with techniques. His criticisms are indictments not of the method but of unacceptable criteria used in interpretation.

# SURGICAL PROBLEMS ARISING DURING PREGNANCY\*

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DURING the past eleven years approximately 40,000 pregnant women have been admitted to the New York Hospital. In this group of patients, 120, or 0.3 per cent, presented surgical or gynecological problems arising during the course of their gestation. These are tabulated together with relevant mortality data in Table I. The authors are well

TABLE I. OPERATIONS PERFORMED DURING PREGNANCY  
NEW YORK HOSPITAL. 1932 TO 1943

OPERATION	NO. OF CASES	MATER- NAL MOR- TALITY	ABORTIONS		FOLLOW-UP		
			DUE TO OPER- ATION	NOT DUE TO OPER- ATION	LOST	FOL- LOW'D	TERM DELIV- ERY
Minor Surgical	16	0	0		0	16	16
Major Surgical (nonabdom- inal)	8	0	0		0	8	8
Major Abdominal (surgical)							
Appendectomy (non-per- forated)	36	0	0		12	24	24
Appendectomy (perforat- ed)	4	2	2		0	2	2
Cholecystectomy (2 ac.; 2 chr.)	4	0	0		1	3	3
Resection of ileum (gan- grene)	1	1	1				
I. & D. intra-abdominal ab- scess	1	0	1			1	
Miscellaneous	6	0	0		0	6	6
Total		3	4		13	60	59
%		3.9	5.3		17.1	78.9	77.6
Major Abdominal (gynecolog- ical)							
Oophorocystectomy	23	0	4	1	3	20	15
Myomectomy	11	0	5	1	0	11	5
Miscellaneous	10	0	1	4	0	10	5
Total	44	0	10	6	3	41	25
%		0	22.7	13.6	6.8	90.8	56.8
Total	120	3	14	6	16	101	84
Surgical and gynecological cases							
Per cent		2.5	11.7	5	13.3	84.1	70

aware of the fact that since this subject has received such extensive consideration in the past, there might be little reason for presenting another relatively small series of cases. However, because the fetal

\*Presented at a meeting of the New York Obstetrical Society, October 12, 1943.



and maternal mortality continues to be relatively high, because the problem has received scant statistical attention in the past few years, and because these patients have all been treated by closely coordinated surgical, obstetrical and gynecological services under a full residency regime, it has been deemed important to record the experiences of this institution.

In order to facilitate the study these cases have been divided into appropriate groups according to the nature of the operation performed.

*I. Minor Surgical Operations.*—This comprises a total of 16 patients upon whom such relatively minor procedures as incision and drainage of an abscess, excision of a benign breast tumor, and ligation and excision of varicose veins, were performed. Local or light gas-oxygen anesthesia was employed in these operations and, as should be expected, there was no associated fetal or maternal mortality. Since these patients failed to present any significant surgical or obstetrical problems they may be dismissed without further discussion.

*II. Major Nonabdominal Operations.*—This next group deserves brief but serious attention. It is composed of eight patients upon whom major, but not abdominal, procedures were performed. These are outlined in Table II, and consist of one radical mastectomy for cancer; two

TABLE II. NONABDOMINAL MAJOR OPERATIONS

OPERATION	NUMBER CASES	MONTH	MORTALITY
Radical mastectomy for cancer of the breast	1	3rd	0
Nontoxic adenomata of thyroid	2	3rd, 5th	0
Melanosarcoma of back, excision	1	3rd	0
Craniotomies	2	6th, 8th	0
Radical mastoidectomy	2	8th, 6th	0
Total	8		0%

thyroidectomies for nontoxic goiter; an extensive excision of a melanosarcoma of the back; two craniotomies, one for chronic arachnoiditis associated with increased intracranial pressure, and one for cerebellar abscess; and two radical mastoidectomies in acutely ill patients. These cases were distributed about evenly from the third through the eighth month of pregnancy, and it is considered significant that, in spite of the seriousness of these operations, all of these women delivered normally at term.

*III. Major Abdominal Operations.*—This comprises the largest single group of patients presenting surgical complications during their pregnancy, and is composed of two types of cases—those operated upon for reasons that may be termed surgical in their nature, and those in which the operative indications were in general gynecological. Since these two groups present a number of fundamental differences they have been considered individually by the authors, the first by C. G. C., the second by R. G. D. All of these cases have been subjected to analysis from the conventional points of view including history, physical examination, laboratory studies, vital signs, anesthesia employed, cultures taken at operation, etc. Since most of these data proved to be of relatively minor

significance, they have been omitted here as being noncontributory to the problem as a whole. Only those features deemed of interest will be considered.

### General Surgical Cases

There were 52 patients in whom the major abdominal operation was performed because of indications which have been termed surgical in nature. The first point of view from which these cases were studied concerns the correctness of the preoperative diagnosis. Excluding 11 cases, such as biliary tract disease, strangulated herniae, and a few others in which the preoperative diagnosis was self-evident, there remains a group of 41 patients. In all of these a clinical diagnosis of acute appendicitis was made prior to operation. This proved to be correct in 25 instances, but incorrect in 16. In other words, a correct preoperative diagnosis was made in all of the patients proving at operation to have had acute appendicitis in one or another of its forms; in sixteen, however, other pathologic entities were found within the peritoneal cavity. A brief summary of these patients will be found in Table III. When one considers the handicaps to accurate surgical diag-

TABLE III. 16 CASES INCORRECTLY DIAGNOSED BEFORE OPERATION  
PREOPERATIVE DIAGNOSIS IN ALL—ACUTE APPENDICITIS

DIAGNOSIS	OPERATION	NUMBER CASES	MONTH	MORTALITY	
				MATER- NAL	FETAL
Twisted ovarian cyst	Resection of cyst	2	4th, 6th	0	0
Chronic appendicitis	Appendectomy	6	2nd thru 8th	0	0
Acute salpingitis, with peritonitis	Appendectomy	1	5th	0	0
Pedunculated myoma, gangrenous	Resection myoma	1	7th	0	0
Acute pyelitis	Appendectomy	2	5th, 6th	0	0
Torsion of fallopian tube	Resection of tube	1	8th	0	0
Gangrenous hydatid of morgagni	Resection hydatid	1	9th (Cesar. sec- tion eclamp- sia)	0	0
Acute gastroenteritis	Appendectomy	2	both 2nd	0	0
		16		0%	0%

nosis which the gravid uterus superimposes upon an already difficult problem, it is perhaps a wonder that the number of inaccuracies was not greater. It is of course gratifying to note that there was no maternal or fetal mortality in any of these patients. The patient in whom a gangrenous hydatid of Morgagni was resected perhaps deserves a further word of comment. She developed her acute abdominal symptoms at term and shortly following operation presented signs and symptoms of eclampsia. It was for this reason that the cesarean section was performed, not because of the surgical procedure or disease.

### Appendicitis During Pregnancy

The largest and most interesting single group of patients in this series is that involving the appendix. The subject of appendicitis in pregnancy has been one open in the past to no small amount of discussion. Much of this can apparently be traced back to the time when the correct treatment of appendicitis itself presented far greater problems than it does today. Appendicitis uncomplicated by pregnancy was a serious and often a lethal disease; and when the pregnant state was added to it, the patient's plight apparently became precarious indeed. Hence, the early literature upon this subject is replete with dire warnings and implications based more upon fear of the combined problems than upon actual knowledge of the various factors involved. The observation that many women died when appendicitis complicated pregnancy or vice versa led to many ill-founded and unfortunate impressions. The high mortality produced a number of beliefs, namely that pregnant women are less well able to withstand infection, that the displaced appendix is more prone to rupture, that the peritoneal cavity is unable during pregnancy to wall itself off adequately, and that the increased vascularity is in itself serious in the presence of an acute septic process. Upon these conceptions was formulated a therapeutic policy which in all likelihood contributed to increase rather than to decrease the high mortality. The early plans of attack involved the principle of removing the appendix and emptying the uterus as nearly simultaneously as possible. This led to such combined operations as cesarean section, followed by exploration of the appendix and its removal, or appendectomy followed promptly by some form of accouchement forcé. These operative procedures, particularly if combined with a sufficiently generous delay during which time the appendix frequently ruptured, proved more than many an unfortunate patient could reasonably be expected to tolerate. It is little wonder that the mortality was high. As time has gone on, however, and knowledge of appendicitis has increased, most of these erroneous impressions have been discarded, and the present approach to the problem of appendicitis in pregnancy adopted. This group of patients has been treated with the principle clearly in mind that the only correct treatment of appendicitis during gestation rests securely upon early operation, and that the pregnancy be allowed to progress undisturbed save for purely obstetric reasons.

In reviewing a number of reports upon this subject two findings have been repeatedly noted;<sup>1-4</sup> one, that by far the greatest number of cases of appendicitis occur during the early months of pregnancy, and two, that when appendicitis does occur late it usually does so in its more severe forms. In this respect this series is no exception; 18 appeared in the first trimester, 12 in the second, and 6 in the last. (Table IV.) Furthermore, three of the four cases in which perforation occurred appear in the last two months and the only two maternal and fetal

TABLE IV. APPENDECTOMY DURING PREGNANCY

MONTH	NORMAL	CHRONIC	ACUTE WITHOUT PERFORAT.		ACUTE WITH PERFORATION		TOTAL PER MONTH
			DIFF. SUPPURAT.	GANGRENOUS	ABSCESS	GEN'L. PERITON.	
1st		2	5		1		8
2nd	2	1	2				5
3rd		4	3				7
4th			5	(2)			5
5th	1 pyelitis	1	2				4
6th	1 pyelitis	1	3				5
7th		1					1
8th			1			2 2 deaths	3
Term		1				1	2
Total	4	11	21		1	3	40

1st trimester 18 cases

2nd trimester 12 cases

3rd trimester 6 cases

deaths are found in the eighth month. A number of explanations have been advanced in the past to account for this phenomenon, most of them involving such vagaries as the early displacement of the appendix precipitating appendicitis, and the lessened ability of the peritoneal cavity to withstand infection in the presence of the gravid uterus, etc. These, however, hardly seem adequate. It is suggested, therefore, that actually appendicitis is quite as common in the last two months as it is earlier but that the diagnosis is far less frequently made. This postulation, which was true in the series of Norton and Connell,<sup>5</sup> seems to be substantiated logically by several facts: First, that the presence of the gravid uterus renders the diagnosis more difficult to make at or near term. Second, the multitude of abdominal signs and symptoms that tend to appear late in pregnancy are often difficult to evaluate correctly. Third, it is well recognized that many attacks of acute appendicitis subside spontaneously. Thus, it seems reasonable to conjecture that a number of attacks of this disease in its acute form pass unrecognized in the seventh, eighth and ninth months. Particularly does this seem to be true when the natural hesitancy of obstetricians and surgeons to complicate a term pregnancy by an operation is appreciated. As far as the greater seriousness of appendicitis late in pregnancy is concerned, the explanation seems apparent, namely that only those attacks progressing to rupture and subsequent peritonitis are recognized.

If this concept be correct, the only course by which the mortality from this disease is to be lowered significantly lies in making a diagnosis early enough to operate upon these patients before perforation has occurred. Particularly is this true when one considers that the mortality in unruptured appendicitis is in this series zero, and among the general population less than 0.2 per cent.<sup>7</sup> The tragic sequelae of perforation can be

prevented only by according abdominal complaints more careful attention during the last trimester, and operating earlier and in greater frequency upon those who might be suspected of having the disease in its simple acute stage. As is adequately demonstrated not only by this but by other series of cases of this type, mothers do not die nor are babies lost as a result of an uncomplicated celiotomy. If the policy of earlier and more frequent operation is adopted for what may seem at the time relatively benign symptoms and signs, it may be anticipated that a certain number of pregnant women will be operated upon needlessly. In view of the all but negligible risk involved, it is apparent that this is a small price to pay compared to the tragedy that follows the rupture of but one appendix. This approach to the general problem of appendicitis is one for which surgeons have not infrequently been criticized. That it has withstood the test of time, however, is reflected in a steadily decreasing mortality rate in appendicitis and that it has a definite place in the armamentarium of general surgery is becoming increasingly obvious. It should, therefore, find a similar application in this disease as it arises during the course of pregnancy.

The next point of interest is found in a consideration of both the immediate and late results in these patients in whom appendectomy was performed during the course of their gestation. The hospital mortality and follow-up results are briefly outlined in Table V. Out of the entire

TABLE V. FOLLOW-UP STATISTICS—40 CASES OF APPENDECTOMY

DIAGNOSIS	NUMBER CASES	HOSPITAL MORTALITY		FOLLOW-UP		MOR- TALITY
		MATER- NAL	FETAL	LOST	TERM. DEL.	
I. Normal	4	0	0	2	2	0
II. Chronic	11	0	0	3	8	0
III. Acute without perforation	21	0	0	7	14	0
IV. Acute with } Perforation } abscess } peritonitis	1	0	0	0	1	0
	3	2	2	0	1	66%
	40	2	2	12	26	

Total Mortality—Maternal 5.0%  
Fetal 5.0%

group of 40 cases, two mothers and two infants were lost, giving a gross mortality of five per cent. In those unperforated there was no maternal mortality nor were there any abortions or premature deliveries. As soon, however, as perforation complicated the picture, two out of the four mothers and their two infants were lost. The two remaining cases with perforation survived, one with a localized abscess occurring in the first month of pregnancy, and one with generalized peritonitis at term. Two out of the three patients with generalized peritonitis at or near term succumbed to their disease giving the high mortality rate of 66 per cent.

Although admittedly this series of cases is small, it lends added credence to the impression that generalized peritonitis at or near term is

a serious problem, any predictions as to the outcome of which must be guarded. Nor is our clinic alone in this experience. Smith and Bartlett<sup>7</sup> in 1940 reported a series of similar cases from the Boston Lying-in Hospital. These authors noted that three of their four cases of perforated appendicitis not only appeared in the last two months, but also died; while the fourth case, a woman four months pregnant, recovered only after a long and stormy course.

### Major Abdominal, Exclusive of Appendicitis

In progressing now to consideration of the remaining patients subjected to a major abdominal operation, the outstanding feature is that by far the greatest number of these individuals presented acute surgical problems demanding more or less immediate operation. These are outlined in Table VI where the relevant statistical data may be found. The

TABLE VI. MAJOR SURGICAL ABDOMINAL CASES, EXCLUSIVE OF APPENDICITIS

DIAGNOSIS	OPERATION	NUMBER OF CASES	MONTH OF PREGNANCY	HOSPITAL MORTALITY		FOLLOW-UP	
				MATERNAL	FETAL	LOST	TERM. DEL.
Acute cholecystitis Cholelithiasis	Cholecystectomy (2)	2	3rd and 4th	0	0	1	1
Chronic cholecystitis Cholelithiasis	Cholecystectomy (2)	2	2nd and 3rd	0	0	0	2
Strangulated hernia	Repairs (3)	3	2nd and 4th and 8th	0	0	0	3
Chronic pyelonephritis	Nephrectomy	1	3rd	0	0	0	1
Ureteral Calculus	Ureterolithotomy	1	5th	0	0	0	1
Acute intestinal obstruction, Perforated Ileum, Intraabdominal abscess	Resection of ileum with drainage	1	6th	1 (19 days p.o.)	1 (1 day p.o.)	Mother and fetus died	
Acute intraabdomin. abscess in Left lower quadrant	Incision and drainage	1	4th	0	1 (3 days p.o.)	Mother discharged well, with fecal fistula, abortion	
Totals		11		1	2	1	8

four patients with biliary tract disease, the three with strangulated herniae, and the two urological problems serve to re-emphasize the point already made that pregnant women can be operated upon with relative impunity. In this group the most interesting cases are the last two. The first of these was referred to the surgical service after having been treated unsuccessfully in two other hospitals for intestinal obstruction due to postoperative adhesions. When first seen she was desperately ill and went on to develop a gangrenous loop of ileum with perforation and multiple intra-abdominal abscesses. One day following resection of the

involved ileum she aborted, and nineteen days later expired in spite of all forms of supportive therapy. This patient presented a complicated surgical problem in which the pregnancy apparently played a relatively minor role. The last patient was explored because of a mass in her left lower quadrant. Following drainage of a large intra-abdominal abscess, the etiology of which was never adequately explained, she was acutely ill. She aborted on the third postoperative day, but ultimately recovered though she was discharged with a fecal fistula.

This group of patients reflect a firmly ingrained tendency not to subject women during gestation to operation unless it becomes imperative. It may be supposed justly that many more pregnant women than are operated upon present themselves during their ante-natal course with chronic surgical disease. Advice is undoubtedly given them to postpone, if possible, any operative intervention until after delivery. Of these it is reasonable to suppose that the majority deliver without developing an acute problem which demands operation. Still there are a significant number who develop an acute exacerbation of their disease, and of these a certain percentage, true it is small, will succumb. Particularly is this true when the disease carries with it the possibility of an associated peritonitis. It is not justified, of course, to interpret this attitude as indicating that all pregnant women presenting surgical problems in a quiescent state should be operated upon. It should mean, however, that operation need not be withheld in those patients presenting a sufficient number of signs and symptoms to make the development of an acute episode a real possibility.

Before leaving the patients who were subjected to abdominal operation primarily upon surgical indications, one significant phase deserves comment, namely, the outlook in the future for patients who, despite having had everything possible done to prevent it, ultimately present themselves with a generalized peritonitis, associated with pregnancy. For several reasons it seems justified to assume that their chances of recovery will be far greater in the future than they have been in the past. First, the greater safety in approaching acute right lower quadrant problems through a McBurney incision has been firmly established. Second, the parenteral and perhaps local use of the sulfonamides will undoubtedly contribute to decreasing the severity of the septic process. Third, the use of continuous enteric suction can be relied upon to improve the treatment of the adynamic type of intestinal obstruction that so frequently follows generalized infection of the peritoneal cavity. And, fourth, an increased understanding of water, electrolyte and protein balance will unquestionably aid these unfortunate patients in overcoming their acute illness. These, combined with a rigid laissez-faire policy from the obstetric point of view, all point toward a lowered mortality in the future.

*Gynecological Cases.*—The next group of cases in which a surgical problem complicated the pregnancy is that in which a major abdominal operation was performed because of the presence of an ovarian tumor,

a myoma, or some other suspected gynecologic lesion. In contrast to the general surgical cases in which the majority of patients presented acute problems, the operations in this group may be considered to have been more of an elective nature.

Corresponding to the minor surgical operations there was a group of patients who were operated upon during pregnancy for minor gynecologic lesions, such as congenital abnormalities, cysts of the lower genital tract, condylomata, etc. Since these procedures were unassociated with any untoward effect upon the course of the pregnancy, they were not considered sufficiently important to merit consideration here in further detail.

The largest single group is composed of 23 patients who were operated upon for removal of ovarian tumors (Table VII). In these there

TABLE VII. OOPHOROCYSTECTOMY DURING PREGNANCY

DURATION PREGNANCY	NO. CASES	ABORTION	END RESULT	PATHOLOGY	
1+	2	0	1 del. at term 1 unknown	Dermoid Simple serous	7 7
2+	10	4 3-11-20-60 days	4 del. at term 2 unknown	Corpus luteum Pseudomucinous Parovarian	4 2 1
3+	4	0	4 del. at term	Papillary serous	
4+	1	0	1 del. at term	cystadenoma	1
5+	3	1 operative abort. (carcinoma)	2 del. at term	Papillary serous cystadenocarcin.	1 1
6+	1	0	1 del. at term	SYMPTOMS	
7+	2	0	2 del. at term	Present Absent	11 12
	23	5	15 del. at term 3 unknown		

was no maternal mortality but there were five abortions, one, an operative abortion in the fifth month, and four, all considered due to the ectotomy, in the first two to two and a half months. In considering this relatively high incidence of abortion of four\* out of 22 cases, two factors must be considered. First, the role of the corpus luteum in maintaining pregnancy. Since it is generally accepted that this plays an insignificant part in maintaining pregnancy after the fourth month attention will be given in this series only to those appearing in the first trimester. In one of these four cases the corpus luteum was removed and abortion occurred on the eleventh postoperative day. In the remaining three, even though the corpus luteum was not disturbed, abortion occurred on the third, twentieth and sixtieth days after operation. In contrast to these there were three patients in whom the corpus luteum was removed but who did not abort. In this connection Andrews et al.<sup>8</sup> reported 13 cases in which bilateral dermoid cysts were removed during the first trimester, of which only two patients aborted. Thus, it seems justified to assume that the corpus luteum of pregnancy may not be essential to the maintenance of pregnancy at this time.

\*One of these four patients was difficult to evaluate because she admitted attempting to induce an abortion prior to operation. Following oophorectomy she was discharged well but was readmitted four days later and aborted on what was actually her twentieth postoperative day.



The second important factor affecting the incidence of abortion involves the problem of the optimum time during pregnancy to subject a patient to oophorocystectomy. It will be noted that all postoperative abortions occurring in this series appear before the third month. Andrews et al.<sup>8</sup> in reviewing the literature from this point of view found the incidence of abortion to be lowest when these patients were operated upon during the fourth month, while the number that occur during the second month was relatively high. As judged from this series and the available literature,<sup>9-13</sup> the safest time during pregnancy to subject patients to oophorocystectomy is either during or after the fourth month.

It is evident from the study of these patients subjected to oophorocystectomy that the incidence of abortion was high, this untoward complication occurring in four out of 22 cases. It is possible that a certain number of these could have been avoided if operation had either not been performed at all or had been postponed until later in pregnancy. When these cases are compared to a similar group already referred to in the surgical cases (Table III), it is found that the acute surgical cases were all operated upon after the fourth month.

Although it may have been possible to postpone operation in some of these patients, fully half of them presented signs and symptoms of sufficient severity to indicate the possibility of torsion of the pedicle having taken place. In them anything but immediate operation would indeed have been hazardous. Furthermore, it is of interest to note that all of the abortions occurred in this half, while there were no abortions in those cases in which oophorocystectomy was performed merely as an elective procedure. In this connection it may be of interest to recall that any intraperitoneal irritation causing stimulation of the gastrointestinal tract may reflexly initiate uterine contractions. In explaining, therefore, why those patients with symptoms abort early in pregnancy, while those without do not, it appears logical that the peritoneal irritation occasioned by a partially ischemic ovarian cyst might well stimulate the uterus either directly or indirectly to empty itself. In none of these patients was progestin therapy routinely employed nor were any consistent efforts made to determine the pregnandiol excretion as has been advised by Nucci<sup>14</sup> and Andrews et al.<sup>8</sup>

An alternate method of course for dealing successfully with patients in whom the pregnancy is complicated by an ovarian tumor is indicated in Section B of Table IV. In all of these patients living babies were obtained by postponing operation till near term, at which time cesarean section was performed. In four cases the cyst was removed at this time, in one it was left in place.

In Table VII the microscopic diagnosis of the ovarian tumors removed is outlined. Seven of the tumors were dermoids, seven were simple serous cysts, two were pseudomucinous and one a parovarian cyst. There was one papillary serous cystadenoma, while in one instance both ovaries were removed for papillary serous cystadenocarcinoma. Four of these tumors measured approximately 6 cm. in diameter, while the other 19 were larger, the largest being 26 cm. in diameter. In one patient no attempt was made to remove a dermoid which was found firmly adherent to the pelvis.

The next group of interest is composed of eleven patients operated upon during the course of their pregnancy for myoma uteri. These are outlined in detail in Table VIII. In two patients exploration alone was performed, myomectomy being deemed inadvisable. Of these two,

TABLE VIII. MYOMECTOMY DURING PREGNANCY

OPERATION	NO. CASES	MONTH PREG.	ABORTED POST- OPERATIVELY	PATHOLOGY	DELIVERY AT TERM
Myomectomy	3	2 or less	3	Degeneration 2 Uncomplicated myoma 1	0
Myomectomy	2	2-4	0	Carneous de- generation	2
Myomectomy not feasible	2	2-4	2 One induced	—	0
Myomectomy	4	4-6	1	Degeneration cystic, hyaline or carneous	3
Total	11		6		5

one aborted postoperatively while the other was discharged well, only to be readmitted a week later having had an abortion induced shortly after leaving the hospital. In the nine patients in whom myomectomy was performed four aborted and five progressed to delivery at term. Myomectomy in this series, therefore, represents an operation, the fetal loss associated with which is exceedingly high.

The explanation for this large number of abortions lies in the excessive amount of uterine manipulation necessary to secure removal of the tumors. For instance, it was found that in those patients who progressed to term the size of the attachment of the myoma to the uterus was never over five centimeters in diameter. In those who aborted, however, the size of the attachment was so large that the uterus was of necessity severely traumatized during the course of the operation.

In studying these patients, therefore, from the point of view of postulating a therapeutic policy which in the future could be expected to result in a lower incidence of fetal loss, several factors immediately presented themselves. In the first place these eleven patients obviously belong to that large general group in which it is recognized that the pregnancy is complicated to a greater or lesser extent by the presence of a myoma of the uterus. It is true that most of these patients can be expected to progress to term without undue difficulty. There will, however, be a few who will present signs and symptoms due to the tumor which are of sufficient severity to make operation all but imperative. This situation presented itself in eight of the 11 patients. In the other three, however, the operative indications were unfortunately merely the presence of a large abdominal tumor unassociated with any real complaints upon the part of the patients themselves. Size alone therefore should not be accepted as a valid reason for operating upon such individuals. These experiences indicate that only those patients should be subjected to myomectomy who present very real and persistent complaints. Particularly is this true when it is appreciated that if the major ante-natal problem associated with the tumor concerns only its potential ability to obstruct the birth canal, cesarean section at term can be relied upon to yield living infants without undue risk to the mother. In this connection those cases have been reviewed in whom section was performed because of the obstructing effect of large myomata. This group of 22 patients is outlined in detail in section A of Table IX. It is interesting to note that all but two were elderly primiparas. There were no babies lost, but one mother, in whom the tumor was not removed, developed a fatal peritonitis.

As in the general surgical group there were a number of patients in this series in whom the preoperative diagnosis was incorrect. These 10 patients are outlined in Table X. In the first case the preoperative diag-

TABLE IX. CESAREAN SECTION

OPERATION	NO. CASES	PATHOLOGY	MATERNAL MORTALITY
A. INDICATION—MYOMATA			
Cesarean section and hysterectomy	7	Degeneration	0
Cesarean section and myomectomy	7	Degeneration	0
Cesarean section; tumor not removed	8	—	1 (Peritonitis)
B. INDICATION—OVARIAN			
Cesarean section Oophorecystectomy	4	Dermoid	0
Cesarean section Cyst not removed	1	Dermoid	0
	27		1

TABLE X. MISCELLANEOUS OPERATIONS DURING PREGNANCY

PREOPERATIVE DIAGNOSIS	NO. CASES	DIAGNOSIS AT OPERATION	MONTH OF PREGNANCY	END RESULT
Myomata uteri	1	Pregnancy	3	Delivered at term
Ectopic pregnancy	3	Pregnancy	1½	Delivered at term
Ectopic pregnancy	3	Incomplete abortion	1½-2	Abortion completed
Endometriosis	1	Pregnancy with adhesions	3	Delivered at term
Extens. adhesions	1	Extensive adhesions	5	Aborted first day
Myomata uteri missed abortion	1	Missed abortion	2 8 mos. amenorrhea	—

nosis was myomata uteri and a normal three months gravid uterus was observed at operation. In the next six cases in which the preoperative diagnosis was ectopic pregnancy, three of the patients were discovered to have a normal intrauterine gestation which progressed to term satisfactorily. In the other three the correct diagnosis was established as an incomplete abortion, all of these requiring a dilatation and curettage. The remaining three cases are self-explanatory. The significant find-

TABLE XI. HYSTEROMYOMECTOMY DURING PREGNANCY

INDICATION	NO. CASES	PATHOLOGY	MONTH OF PREGNANCY
Pregnancy not recognized	6	Uncomplicated myomata 5 Hyaline degeneration 1	Less than 7 weeks
Pregnancy suspected or known	4	Uncomplicated myomata	1½ to 2½ months
Renal disease	2	Uncomplicated myomata	2-3½ months

ing in this group of patients is that when a diagnosis of ectopic pregnancy cannot be made in any other way than by operation, simple exploration can be performed without incurring any excessive risk.\*

### Conclusions

Several conclusions of significance appear warranted from study of these patients.

1. Pregnant women tolerate even major surgical procedures quite as well as the nonpregnant.

2. When the surgical disease, however, becomes complicated by peritonitis, the outlook is unfavorable, and the maternal and fetal mortality, high.

3. Ovarian tumors complicating pregnancy may be removed with relative impunity provided operation can be postponed until after the first trimester.

4. Myomectomy should not be performed during pregnancy except upon urgent indications.

5. An exploratory celiotomy for suspected ectopic pregnancy may be performed with relatively little danger of interrupting a normal intra-uterine pregnancy should the preoperative diagnosis fail to be substantiated.

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### Discussion

DR. JAMES R. MILLER.—A number of years ago I reviewed the dermoid cysts seen at the Hartford Hospital. About every sixth patient had multiple dermoids. In one case which necessitated the removal of one ovary entirely because of torsion, the corpus luteum of pregnancy in the other ovary lay between two other dermoid cysts. It was possible to shell the dermoids out by careful dissection. The patient went to term and was delivered of a live baby.

Recently in the Hartford Hospital, we had a patient, six months pregnant, who had had a previous gynecologic operation. She had partial and then complete obstruction over a period of about seven days. About three feet of bowel were resected and an ileostomy was done, which was closed later. She also went to term.

\*Although not strictly relevant to the topics discussed in this paper 12 patients in whom hysteromyomectomy was performed during pregnancy are outlined in Table XI. They are included here for the sake of completeness, although actually they did not constitute a surgical complication during pregnancy. The pregnancy was terminated by the very nature of the operation.

DR. MORTIMER D. SPEISER.—At the French Hospital there have been five cases of acute intestinal obstruction complicating pregnancy in the first 6,822 obstetric admissions. Four of the cases followed a previous laparotomy, one for multiple myomectomy, another for an appendectomy and Baldy-Webster suspension, and two for a simple appendectomy without drainage. The fifth case, without a previous history of a laparotomy or pelvic inflammatory disease, was due to a volvulus of the sigmoid.

Unfortunately, when the classical symptoms of ileus arise during the course of a pregnancy they do not always receive the serious consideration which they merit. The periodic cramplike pains are frequently considered to be the result of uterine rather than intestinal contractions. The painful sensation should be synchronous with palpable uterine contractions if the uterus is palpable above the symphysis. Nausea and vomiting may occur at any time during the course of pregnancy, but it is especially significant that it is most prevalent during the first trimester of pregnancy when intestinal obstruction is least common. Constipation is very frequent in the female and almost universal during pregnancy, but if in addition to this, repeated enemas are ineffectual and do not relieve the pain and distention, acute intestinal obstruction must be considered. Furthermore, rapidly increasing tympanitic abdominal distention, with pain and obstipation, must have some mechanical basis. For confirmation one may resort to roentgenologic studies. The characteristic picture of small bowel obstruction is sufficiently pathognomonic, but the absence of such findings cannot be interpreted as ruling out this complication. The use of a Miller-Abbott tube may be a distinct aid to such a diagnosis. Again, large bowel obstruction is readily visualized on roentgenographic studies with the use of a barium enema if necessary.

As the result of early diagnosis followed by adequate preoperative and operative care, there was no maternal mortality in our five cases. In four of the patients it was necessary to do an hysterotomy in order to explore the abdominal contents adequately. This procedure, unfortunately, accounted for three fetal deaths due to prematurity. In only one instance, which occurred in a pregnancy of three and one-half months' gestation, were we able to leave the uterus unmolested.

DR. WILLIAM E. STUDDIFORD.—I did not hear Dr. Child say anything particular in regard to the site of the incision for appendectomy during pregnancy. I had difficulty in approaching the appendix with an eight months' pregnancy obstructing the operative field. In the particular case to which I have referred, we used a muscle-splitting incision, the center of which was about halfway between the anteriorsuperior spine and the costal margin. With this incision the top of the right broad ligament came into view and the uterus lay just to the left. With a deep right-angled retractor, it was possible to pull the broad ligament down and the uterus to one side, bringing the appendix into view. It was removed then without any difficulty.

DR. SAMUEL A. COSGROVE.—Our incidence of these surgical complications of pregnancy has not been as high as those at the Lying-in Hospital. At the Margaret Hague Maternity we have had 29 cases of acute appendicitis, several of which were characterized by gangrene or rupture of the organ, five by generalized peritonitis. Twenty-four occurred before the seventh month; five beyond the seventh month and two were actually intrapartum.

In 13 other cases the appendix was removed during pregnancy. These were removed either when associated with other pathology or some as a result of error in diagnosis. Of this total of 42 cases one mother died, a late case of generalized peritonitis, giving a mortality rate of 4.2 per cent. Five fetuses were lost, two of which were inevitably compromised before operation, a mortality of 12 per cent.

Our number of ovarian cysts and fibromas has not been as large as the Lying-in Hospital series, perhaps because of a little more conservative tendency on our part. We have had 17 cases of ovarian and parovarian cysts, with no maternal mortality, but with 41.2 per cent fetal loss. This is comparable to that of Dr. Child and Dr.

Douglas. There were 10 cases of uterine fibroids, with no maternal mortality, but with a 60 per cent fetal loss, which is comparable to theirs.

We had six cases of thyroidectomy, with no maternal or fetal loss.

We do not feel that the difficulty of diagnosis is greater in the pregnant than in the nonpregnant. About the only specific diagnostic evidence that one can depend upon in estimating acute appendicitis is localized, persistent tenderness. We have not found so much dislocation of the area of tenderness as other observers have and we feel that we can make a reasonably sure diagnosis of appendicitis without depending on a triad or any other combination or syndrome which so often does not exist. The operation itself is not serious, as has been demonstrated by the results which have been reported here this evening. Just the other day we had a patient who delivered a seven months' fetus four days after an appendectomy for an acute catarrhal appendicitis. The wound does not apparently suffer any particular stress; there is no more danger of dehiscence because the woman goes into labor immediately or a short time after operation than under any other circumstances. Therefore, in view of the well-taken point that in late pregnancy the progress of acute appendicitis may be more malign and rapid than it is in the nonpregnant, it is just as appropriate to operate on a few of these cases on suspicion as if a similar situation occurred in the nonpregnant woman.

There is one type of case in which I would recommend conservatism in acute appendicitis and it may be the answer to part of our mortality. That is the advanced case of general peritonitis. Some of those cases are, from a surgical viewpoint, not operable and do better if treated conservatively. This is hardly the place to develop that thesis, but I would commend to your attention the very occasional case which will do better on a strict Ochsner regimen and entire dependence, for a considerable period of time if necessary, on parenteral maintenance of water, electrolyte and protein balance.

DR. GEORGE W. KOSMAK.—I would like to ask Dr. Douglas if they encountered among these surgical complications any ureteral calculi. I remember one case at the Lying-in Hospital many years ago where the patient had a ureteral calculus on the right side, causing obstruction and giving rise to symptoms very similar to an appendicitis. The patient was operated upon and a calculus about one inch long taken from the ureter in the seventh month of pregnancy. The patient went on to full term.

DR. ALFRED C. BECK.—For a number of years we have been very conservative at the Long Island College Hospital in the treatment of fibroids complicating pregnancy. Formerly in Doctor Polak's time some myomectomies were done. During the past ten years, however, I cannot recall a single case in which we thought myomectomy was necessary. Occasionally these tumors become very painful but they respond to conservative treatment.

If a cesarean section is necessary for obstruction due to a fibroid in the lower uterine segment, we believe that the fibroid should not be left behind. The cesarean section accordingly should be followed by hysterectomy or the tumor should be removed by myomectomy. Otherwise a tumor which is large enough to interfere with the passage of the child will interfere with drainage from the uterus and consequently lead to subsequent difficulty.

DR. CHILD (closing).—Intraperitoneal drainage is instituted in all cases of acute appendicitis in which free perforation has taken place. Occasionally, in cases of gangrenous appendicitis without perforation the parietal wall alone is drained, that is, down to the peritoneum. In the four cases in this series in which generalized peritonitis was present drainage was instituted.

In all cases in which appendicitis was suspected the peritoneal cavity was entered through a McBurney type of incision. The midpoint of this incision is usually placed over the point of maximum tenderness. The advantages of this type of incision, particularly if perforation has taken place, are too well known to require repe-

tion here. If, on the other hand, the preoperative diagnosis is found to be incorrect and one of the rectus incisions is needed, the additional trauma of the McBurney incision is not considered particularly detrimental to the patient.

The so-called Ochsner form of treatment is not customarily employed at the New York Hospital. This does not mean, however, that a reasonable amount of time is not allowed to prepare adequately an acutely ill patient for operation.

We have not encountered any patients in whom a right renal calculus was mistaken for acute appendicitis.

DR. DOUGLAS (closing).—Dr. Bishop's question with relation to the incidence of myomectomy at the present time as compared to former experience is difficult to prove statistically in a small series of cases. It is my impression that we are interfering less frequently now than formerly. Actually only one case has been operated on since 1939. I was interested in hearing Dr. Beck say that they have not had occasion to perform a myomectomy recently. I have reviewed one of Dr. Polak's papers on the subject and the incidence of myomectomy was obviously higher then than it is at this time.

In regard to Dr. Kosmak's question with reference to ureteral calculi, there was a considerable number of patients with this complication who were not subjected to operation during pregnancy and who are not included in this study.

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Kloman, Erasmus H.: *Vesicovaginal Fistula*, South. M. J. 34: 271, 1941.

The author briefly reviews the history of operations for the cure of vesicovaginal fistula, indicating the significant contributions to the procedure in the successive stages of its development. Modern technique, it is emphasized, is based upon the work of pioneer surgeons. He makes the distinction between "present-day" gynecologic fistulas, which result from pelvic operations, the use of radium, and the cautery, and obstetric fistulas which develop consequent to the trauma of labor and parturition. The postoperative fistulas contrast with the latter in that they are usually high in the vaginal vault and of difficult access. Accordingly, the author employs the knee-chest posture for this operation, stressing the advantages of better exposure of the operative field, with the surgeon working down upon the latter rather than up under the pubic rami, decreased vascularity and relative anemia of the elevated tissues.

The patient is anesthetized in the usual dorsal position, then turned to the prone position and elevated to the knee-chest posture by a special device which may be adapted to any operating table. This position may be maintained indefinitely. A method whereby the fistula may be drawn down closer to the introitus in order that its dissection and repair may be facilitated, is an original contribution of the author. This is accomplished by the use of 6 to 8 traction sutures of stainless steel wire which are introduced through the vaginal mucosa and submucosa about 2 cm. from the periphery of the fistula orifice, and held with clamps. The method obviates the necessity for using metal retractors which may offer obstruction. Preliminary to operation, any existing urinary tract infection must be cleared. The relationship of the fistula to the urethra and the ureters should be determined; if the proximity of the ureteral orifice is close, a catheter may be passed, or transplantation of the ureter performed.

Complete separation of the vaginal mucosa and the bladder is essential so that the closure may be accomplished with a minimum of tension. For the vesical wall a purse-string catgut suture reinforced by a second layer of continuous suture is employed. Apposition of the vaginal flaps is accomplished with nonabsorbable fine dermal sutures which remain four weeks. Postoperatively, the patient is placed in a prone position and a self-retaining urethral catheter provides for bladder drainage and for twice daily irrigation. Acidification of the urine tends to prevent crust deposits.

ARNOLD GOLDBERGER.

# CARCINOMA OF THE CERVIX COINCIDENT WITH PREGNANCY\*

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THE literature dealing with carcinoma of the cervix coincident with pregnancy consists for the most part of reports of a single case or of statistics assembled by a number of authors from these reports. There is little agreement concerning frequency, behavior, treatment or the prognosis of carcinoma associated with pregnancy.

## Material

This study was made to determine as accurately as possible the incidence of pregnancy in approximately 3,500 cases of carcinoma of the cervix observed at the Mayo Clinic in nearly thirty-two years, that is from July 1, 1909 to February 28, 1941, inclusive, and to ascertain whether or not the prognosis of the disease is modified by the co-existent pregnancy. It was considered of interest to investigate the possibility that gestation may occur in the presence of an established carcinoma of the cervix. The results of therapy were reviewed in an effort to determine the method or methods of choice in the treatment of carcinoma of the cervix coincident with pregnancy.

In twenty-six, or 0.7 per cent, of the 3,570 cases of carcinoma of the cervix, the patients also were pregnant. In forty-five other cases there was a close association between pregnancy and carcinoma of the cervix but the coexistence of these two conditions could not be proved absolutely; therefore, these cases were excluded from consideration. We shall attempt to correlate the findings in these twenty-six cases with the findings in the cases reported in the literature.

## Incidence

In the reports in the literature, the stated incidence of carcinoma of the cervix among pregnant women has varied. However, examination of a number of such reports indicates that the incidence is in the neighborhood of 0.05 per cent. Thus, when one considers the frequency of pregnancy, a complicating carcinoma of the cervix is not an extremely rare occurrence.

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†Partial abridgment of thesis submitted by Dr. Maino to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery. Dr. Maino is now on active service in the Medical Corps of the United States Navy.

††The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.



TABLE I  
CLINICAL AND PATHOLOGIC FINDINGS, TREATMENT AND RESULTS

CASE	YEAR OF OBSERVATION	AGE YEARS	GRAVIDA	PARA	STAGE OF PREGNANCY	MALIGNANT LESION		GRADE	DURATION OF SYMPTOMS	TREATMENT	RESULTS, INTERVAL AFTER TREATMENT	
						TYPE	STAGE				ALIVE	DIED
1	1909	33	5	3	Term	No report	4		4 mo.	Porro's cesarean operation; subtotal hysterectomy		3 days
2	1912	31	8	4	Term	Squamous cell epithelioma	2	4	5 mo.	Cesarean section; total abdominal hysterectomy		9 mo.
3	1915	33	5	2	30 wk.	Squamous cell epithelioma	2	3	6 mo.	Total abdominal hysterectomy	23 yr.	
4	1916	36	5	5	Term	Squamous cell epithelioma; adenocarcinoma	2	3	Post-partum	Vaginal hysterectomy		15 mo.
5	1916	35	7	5	16 wk.	Squamous cell epithelioma	2		9 mo.	Radium and roentgen therapy		8 mo.
6	1916	40	8	8	Term	Squamous cell epithelioma	3		6 mo.	Radium and roentgen therapy		8 mo.
7	1917	34	11	3	6 wk.	Squamous cell epithelioma	1	4	7 mo.	Vaginal hysterectomy; radium and roentgen therapy	12 yr.	
8	1918	35	2	1	18 wk.	Squamous cell epithelioma	4	3	2 yr.	Total hysterectomy; radium and roentgen therapy		6 yr.
9	1919	37	11	11	Term	Squamous cell epithelioma	3		2 mo.	Porro's cesarean operation; radium therapy		4 mo.
10	1919	28	7	5	18 wk.	Squamous cell epithelioma	2	4	5 mo.	Total abdominal hysterectomy; radium therapy		4 mo.
11	1919	26	5	4	Term	Squamous cell epithelioma	1	4	1 yr.	Vaginal hysterectomy; radium and roentgen therapy		2 yr.

12	1920	29	5	4	32 wk.	Squamous cell epithelioma	4	3	4 mo.	Cesarean section; subtotal hysterectomy; radium and roentgen therapy	1 wk.
13	1922	28	4	3	25 wk.	Myxosarcoma*	1	3	1 yr.	Subtotal hysterectomy	1 yr.
14	1928	32	2	1	10 wk.	Squamous cell epithelioma	3	3	6 mo.	Radium and roentgen therapy	11 yr.
15	1928	39	13	11	6 wk.	Adenocarcinoma	2	2	1 yr.	Total abdominal hysterectomy; radium and roentgen therapy	10 yr.
16	1928	27	5	4	18 wk.	Squamous cell epithelioma	2	4	2 mo.	Total abdominal hysterectomy; radium and roentgen therapy	11 yr.
17	1928	34	7	2	16 wk.	Squamous cell epithelioma	1	4	6 mo.	Total abdominal hysterectomy; radium and roentgen therapy	11 yr.
18	1932	27	2	1	Term	Squamous cell epithelioma	4	3	2 mo.	Radium therapy	5 mo.
19	1932	32	2	2	Term	Squamous cell epithelioma	3	3	9 mo.	Radium and roentgen therapy	10 mo.
20	1934	28	3	2	20 wk.	Squamous cell epithelioma	3	4	1 yr.	Cesarean section; radium and roentgen therapy	22 mo.
21	1936	35	1	0	8 wk.	Adenocarcinoma	1	2	0	Total abdominal hysterectomy; radium and roentgen therapy	2 yr.
22	1937	34	7	3	27 wk.	Adenocarcinoma	1	1	1½ yr.	Wertheim's operation (1939); radium and roentgen therapy	2½ yr.
23	1939	26	3	1	15 wk.	Squamous cell epithelioma	3	3	6 mo.	Radium and roentgen therapy	Not traced
24	1939	31	2	2	Term	Squamous cell epithelioma	2	3	14 mo.	Porro's cesarean operation; subtotal hysterectomy; radium and roentgen therapy	1 yr.
25	1940	25	3	2	10 wk.	Squamous cell epithelioma	2	4	3 mo.	Wertheim's operation; radium and roentgen therapy	5 mo.
26	1941	41	9	6	14 wk.	Squamous cell epithelioma	1	4	1 yr.	Wertheim's operation; radium and roentgen therapy	2 mo.

\*This paper deals prevalently with earchinomas; this one case of myxosarcoma was not excluded from the series.

As an incidental finding in cases of carcinoma of the cervix, on the other hand, pregnancy occurs with surprising frequency. Incidences of from 0.3 to 5.1 per cent have been given by various authors. The experience of most men, however, would agree to an incidence of about 1.5 per cent. As previously stated, pregnancy also was present in twenty-six, or 0.7 per cent, of 3,570 cases of carcinoma of the cervix observed at the clinic. Since all of these patients came to the clinic because of carcinoma of the cervix and not because of pregnancy, this percentage does not indicate the true incidence of carcinoma of the cervix among pregnant women. In the years 1910 to 1941, inclusive, 8,500 women registered at the clinic because of pregnancy and carcinoma of the cervix was not observed in any of these women.

### Age of Patients

The youngest patient in our series of twenty-six cases was twenty-five years of age and the oldest was forty-one years of age (Table I). There appears to be very little predilection for carcinoma of the cervix coincident with pregnancy to occur at any particular age since there were almost equal numbers of patients in each five-year age group. The average age of the patients was 32 years. The average time at which the carcinoma of the cervix was discovered was in the twenty-fourth week of pregnancy.

### Gravidity

In only one instance did carcinoma occur in the first pregnancy; in five cases it was discovered in the course of the second pregnancy. The greatest number of pregnancies in any one case was thirteen (Table I). In the entire group of cases the average number of pregnancies was 6 and the average number of children was 4.

It has been stated that pregnancy may supervene in a case of established carcinoma of the cervix. In three cases in this series, the pregnancy almost certainly occurred after carcinoma of the cervix was present; in a fourth case, there was definite proof that the carcinoma antedated the pregnancy. In case 14, carcinoma stage 3 was discovered in the tenth week of pregnancy. It is reasonable to suppose that carcinoma of such an advanced stage had been present much longer than ten weeks and that the pregnancy occurred after the carcinoma was well established. A similar reasoning may be applied in case 15, in which carcinoma stage 2 was found in the sixth week of pregnancy. This was the earliest stage of pregnancy at which carcinoma was discovered in this series of cases.

In another case bleeding from the cervix occurred in the eighth month of pregnancy, in December, 1920. The patient had been told that she had a "slight growth on the cervix." A few weeks later, growths protruded from the vagina and there was much foul, bloody discharge. In May, 1921, polyps were removed, only to return four months later; they

were removed again in October, 1921. When the patient first was seen at the clinic in February, 1922, fourteen months after the discovery of the tumor, she again was pregnant; at this time she was in the fifth month of pregnancy. She had a large cervical tumor which proved to be a myxosarcoma grade 3. Undoubtedly these recurring tumors were myxosarcomas and she twice became pregnant during the course of the disease.

Definite proof that carcinoma may antedate conception is furnished by case 22. In October, 1937, the patient aborted a fetus of about one month. Curettage was performed and a biopsy disclosed carcinoma of the cervix. In June, 1938, she was re-examined and radium therapy was prescribed. In July, 1938, biopsy of a large section of the cervix again disclosed papillary adenocarcinoma. In September, 1938, about a year after biopsy first had disclosed carcinoma, she again became pregnant.

### Symptoms

The symptoms of carcinoma of the cervix coincident with pregnancy are those of carcinoma of the cervix plus the symptoms of pregnancy. All authors agree that vaginal hemorrhage is the most common symptom of carcinoma of the cervix. The bleeding may consist only of postcoital spotting. On the other hand, it may not be associated with trauma and may be profuse. An aqueous, odorous discharge commonly is a late symptom. Bleeding was the initial symptom in twenty-three, or 88 per cent, of the twenty-six cases in this series. In most of the cases the patients had had symptoms for two to six months before the diagnosis was made; three patients had not had any symptoms. The average duration of symptoms was 7 months. In one case abnormal bleeding had occurred for one year and in another case it had occurred for two years.

Gross, as well as other authors, found that the duration of symptoms of carcinoma of the cervix was shorter in cases in which the women were pregnant than it was in cases in which the patients were not pregnant. In a series of cases reported by this author, the duration of symptoms was as follows: three months in cases in which the patients were pregnant and 8 months in cases in which the patients were not pregnant. In almost a fifth of the reported cases the symptoms of carcinoma antedated pregnancy.

### Diagnosis

We agree with Rochet's statement that the diagnosis of carcinoma of the cervix coincident with pregnancy often is missed because of the fear of making a pelvic examination during pregnancy. He urged the making of a pelvic examination in any case in which a malignant lesion of the cervix is suspected. He also recommended biopsy and said that this

procedure is associated with little risk even in cases in which the patients are pregnant.

The literature contains reports of several cases in which carcinoma of the cervix has been mistaken for threatened abortion or placenta previa. Carcinoma of the cervix is more likely to bleed as the result of trauma whereas in cases of placenta previa profuse bleeding occurs without apparent provocation. Carcinoma of the cervix is hard and indurated while the cervix of the normal pregnant uterus is soft and velvety.

At this point it perhaps might be advisable to mention the possibility of confusing carcinoma with the hypertrophic changes in the cervix of a pregnant uterus. Clinically, in the presence of pregnancy, the cervix may on occasion appear sufficiently abnormal to cause one to suspect the presence of a malignant lesion. An experienced pathologist would recognize the histologic appearance of tissue obtained by biopsy from the cervix in a case of normal pregnancy as opposed to that of carcinoma.

### Treatment

Previous to 1880, the treatment of carcinoma of the cervix associated with pregnancy was purely symptomatic. The pregnancy was allowed to go to term; artificial methods of delivery were used only in cases of arrested progress. Then cautery, local excision of the obstructing tumor, multiple cervical incisions, manual dilatation, version and extraction, or forceps delivery became the procedures usually employed.

In 1881, Spencer Wells did the first hysterectomy for carcinoma of a known pregnant uterus. By 1909, the year Williams published his excellent article on the subject, several choices of operation were possible. About 1910, when abdominal hysterectomy had become comparatively safe, the radical operation of Wertheim, with or without cesarean section, became the method of choice in cases in which the lesion was operable.

*Surgical Treatment.*—In nine of the thirteen cases observed in the years 1909 to 1927, inclusive, the cervical lesion was considered operable, stages 1 or 2, when the patients first were observed. Radical operation was performed in seven of the nine cases; total hysterectomy was performed in one of these cases (Case 8) two years before admission to the clinic. In three of the eight cases the patients were in an advanced stage of pregnancy, which ordinarily makes the prognosis poor. Of the seven patients, only two remained free of recurrence.

The cervical lesion was found to be operable in eight of the thirteen cases that were observed in the years 1928 to 1941, inclusive. Total hysterectomy was employed in seven of the eight cases. When the seven patients last were heard from, all of them were living; however, only three of the patients had been followed for five or more years after operation.

Cesarean section was performed in six cases. In four of these cases it was followed by subtotal hysterectomy and in another case by total hysterectomy. Although irradiation also was used in four of the six cases the results were not good. The lesions were well advanced at the time of operation and none of the patients lived for five years after the operation.

Total abdominal hysterectomy was performed in eleven cases (Cases 2, 3, 8, 10, 15, 16, 17, 21, 22, 25 and 26). In seven of these cases, more than ten years have elapsed since the operation was performed. In four of the seven cases, the patients were alive when this paper was written; therefore, the ten-year survival rate in the seven cases was 57 per cent; this figure represents the survival rate in cases in which the stage of growth permitted radical operation.

The technique of the Wertheim operation was employed in nearly all of the total hysterectomies, and in three cases (Cases 22, 25 and 26), which were observed more recently the operation was defined as a Wertheim hysterectomy. Although the results so far have been good in these three cases, the time that has elapsed since operation was performed is not sufficient to permit one to say that the patients probably have been cured.

Vaginal hysterectomy was performed in three cases (Cases 4, 7 and 11). In one case it apparently effected a cure.

In the first few cases in this series, the actual cautery was applied to the malignant lesion before the uterus was removed; however, this procedure apparently was of little benefit.

*Irradiation Therapy.*—With the advent of roentgen therapy, opinion became divided as to the relative value of surgical and nonsurgical treatment. Since there was some hope of obtaining a viable infant in cases in which roentgen therapy was employed, personal and religious sentiments in this regard became manifest. The French literature, especially, favored preservation of the fetus by using roentgen therapy until the viability of the fetus was assured.

Irradiation therapy frequently has been used in an attempt to control the growth of the carcinoma until the child has become viable. This is not without risk to both mother and child. Murphy (Schmitt), and other authors have revealed that abortion occurs in about 24 per cent of cases in which this type of therapy is used and that in about 24 per cent of the remaining cases the offspring are defective; about half of the defective infants are microcephalic idiots. This predominance of microcephalic idiocy has been a constant finding among irradiated fetuses. A child often is reported apparently normal at birth, but a follow-up study frequently shows that it died soon afterward, or that after a lapse of from four to seven years its faulty development became manifest.

The importance of this sequel to irradiation during pregnancy has assumed medicolegal significance. Recently, an adverse decision was rendered in suit for damages against a physician because a microcephalic idiot was born to a woman whom he had irradiated early in the course of pregnancy. The pregnancy had not been recognized until after irradiation had been employed.

Rev. P. A. Finney and other moral theologians agreed that, as long as the treatment is directed primarily against the carcinoma which threatens the mother's life, the death of the fetus is secondary and indirect. The church condones the removal of the pregnant uterus for carcinoma of the cervix. In spite of the prevalence of this sound opinion, treatment in many instances is influenced by personal or religious interpretation.

The majority opinion of the past fifteen years favors, when possible, immediate radical removal of the uterus and the subsequent use of irradiation therapy. The results of operation performed in the course of pregnancy are more satisfactory than are the results of operation done after delivery. Nearly all authors agree that vaginal delivery of the fetus increases the immediate mortality of both mother and child and that the ultimate prognosis is likewise made worse.

Irradiation was not employed in the first three cases of this series as these cases were observed prior to 1916, that is before irradiation was widely used either alone or in conjunction with operation in the treatment of carcinoma.

Radium was the principal therapeutic agent employed in ten cases (Cases 5, 6, 9, 12, 14, 18, 19, 20, 23 and 24). In two of these cases (Cases 9 and 24), Porro's operation preceded radium therapy and two other cases (Cases 12 and 20) radium therapy was employed after cesarean section was performed. No surgical operation was performed in the remaining six cases. The lesion was considered operable in only one of these six cases, namely, Case 5. The fact that the patient in this one case died cannot be used to condemn the use of irradiation in the treatment of carcinoma of the cervix coincident with pregnancy. In one of the six cases (Case 14), more than eleven years have elapsed since the patient was treated and there has been no recurrence of the carcinoma. In this case, the carcinoma was classified as stage 3.

In two cases (Cases 23 and 24) which were observed recently, the lesion has not responded well to irradiation therapy. In one case (Case 23) the disease was progressing rapidly when the last follow-up was obtained. In the other case (Case 24), the carcinoma was in a rather early stage of development when the patient first was seen at the clinic but it progressed rapidly to stage 4 while the patient was undergoing treatment. The later use of roentgen therapy produced some symptomatic improvement.

Abortion occurred in all cases in which irradiation was applied to the pregnant uterus. In five of the cases, irradiation therapy was begun in the post-partum period. Vaginal or cesarean delivery had resulted in a living child in all of these cases. In four of the five cases, the mothers died of carcinoma; in the remaining case, the lesion was progressing rapidly when follow-up data last were obtained.

In seven of the ten cases in which irradiation was employed, roentgen therapy was used in conjunction with radium therapy. In two of the three cases in which roentgen therapy was not employed (Cases 9 and 10), the patients refused to undergo further treatment; in the remaining case (Case 18), it was felt that only palliative radium therapy was justified.

### Results and Prognosis

In twelve of the twenty-six cases, the patients were alive when the last follow-up data were obtained; however, in six of these cases, the patients have not been followed for five years. In two of these six cases, the disease apparently has made considerable progress and the prognosis was considered unfavorable when the last follow-up data were obtained. In the remaining four cases, the patients apparently were free of recurrence of the lesion, two and a half years, two years, five months, and two months respectively after they were dismissed from the clinic.

In twenty cases, at least five years have elapsed since the patients were treated at the clinic. Of these twenty patients, six were living and fourteen were dead when the last data were obtained. One of the patients died of an accidental injury but she had no recurrence of the carcinoma for two years after she was treated at the clinic. Thirteen patients died of extension of the malignant lesion. One patient lived six years but had a recurrence of the lesion before five years had elapsed. Of the patients who are alive, one has lived for twenty-three years after treatment, one has lived for twelve years, three have lived for eleven years and one has lived for ten years, without evident recurrence. A cure apparently was obtained in six, or 30 per cent, of the cases in which the patients have been followed for five or more years. If the case in which the patient died accidentally were omitted from these twenty cases, this percentage would be increased to 32.

*Effect of Pregnancy on Carcinoma.*—Whether carcinoma is stimulated, retarded, or unaffected by the coexistent pregnancy is a subject of dispute. There are well-substantiated reports which reveal tremendous acceleration in the growth of the carcinoma; others equally verified have demonstrated a marked inhibitory effect on the progress of the malignant lesion.

The cause of the rapid progress of the carcinoma is not known. It has been suggested that an increase in metabolism, hypercholesteremia, hyperemia, increased amount of glycogen in the cells, "looseness of tissue,"



or increased lymph supply consequent to pregnancy favor the growth and dissemination of the carcinoma. Cervical lacerations attendant on parturition are generally conceded to encourage a rapid spread of the carcinoma.

Gross and Zweifel, quoted by Bainbridge, early in their experience expressed the opinion that pregnancy accelerated the growth of carcinoma but they later changed their opinion to affirm the retarding effect of pregnancy upon carcinoma. Peller was able to demonstrate that in cases of carcinoma of the cervix in which the patients are of equal age the mortality rate is lower in cases in which the patients are pregnant or in the puerperium than it is in the cases in which the women are not pregnant. Bowing showed a significantly better prognosis for women who had been pregnant. Twenty-seven and seven-tenths per cent of women who had been pregnant obtained good results from therapy while the five-year survival rate was only 20.6 per cent for women who had never been pregnant.

Emge's experience with six pregnant patients indicated that the chance of cure of cervical carcinoma coincident with pregnancy was increased above the average.

Stöckl expressed the opinion of many authors in so far as he found no significant alteration in the behavior of carcinoma because of pregnancy, although he recognized individual cases in which the growth of the lesion was apparently stimulated or retarded.

In this connection the work of Slye is most interesting. She observed that when female mice were constantly pregnant energy was withheld from the tumor, which then grew with extreme slowness. If, however, there was an interval between pregnancies, or a termination of pregnancy, the energy which was running into reproduction was released and diverted into the tumor, which then grew more rapidly. During the six or eight days a female mouse is nonreproductive, the tumor grows much more rapidly than it does during the total eight months or a year that she is reproductive. If the tumor antedates the impregnation considerably, the currents of energy are with difficulty diverted to the pregnancy, and probably never wholly so. Hence, when the tumor growth is well advanced before impregnation, rarely are any offspring born; when offspring are delivered, they are likely to be small and undernourished and are rarely suckled.

*Effect of Carcinoma on Pregnancy.*—Sterility, on the basis of a co-existent endometritis, is generally considered to prevail in cases of carcinoma of the cervix. However, the presence of carcinoma of the cervix does not preclude the possibility of a subsequent pregnancy. Even a second pregnancy during the course of development of carcinoma of the cervix has been reported several times, and Basden collected twelve reported cases in which conception occurred after irradiation therapy.

If the carcinoma is untreated and if the pregnancy is allowed to continue, the pregnancy will proceed to full term in about two-thirds of the cases, but only a third of the infants will survive delivery by the vaginal route.

The child of a carcinomatous mother is not likely to be retarded or below normal viability unless the mother is cachectic. The experimental work of Slye supports this opinion.

In fifteen of the twenty-six cases, the pregnancy terminated prior to viability of the fetus. Spontaneous abortion occurred in one of the fifteen cases; in the remaining fourteen cases, the pregnancy was terminated by surgical intervention or irradiation therapy. In two of the eleven cases in which the fetus was viable, a premature infant was delivered in the course of a surgical procedure; in the remaining nine cases, pregnancy progressed to full term.

Of the six patients who lived ten years or more, three were in the first trimester of pregnancy when the carcinoma first was discovered, two were in the second trimester, and one had just entered the third trimester. None of the patients who carried the fetus to or nearly to term lived more than two years. When the diagnosis of carcinoma was made, the pregnancy had reached term in only one, or 14 per cent, of the seven cases in which the lesions were classified as stage 1. When the diagnosis was made, the pregnancy was at or near term in three, or 33 per cent, of the nine cases in which the lesion was stage 2, in three, or 50 per cent, of the six cases in which the lesion was stage 3, and in three, or 75 per cent, of the four cases in which the lesion was stage 4. Although the number of cases in this series is small, these figures strongly suggest that carcinoma of the cervix becomes progressively more severe as pregnancy advances. The number of pregnancies did not influence the prognosis. In cases in which the patients lived ten or more years, the average number of pregnancies was seven, which corresponds closely with the average number of pregnancies in the entire series of cases.

*Fetal Prognosis.*—According to Danforth, Cornil reported the only case in which carcinoma is known to have affected the fetus directly. In this case, metastatic lesions were found in the frontal bone, patella, peritoneum and thyroid gland of the fetus.

The medical literature of the last quarter of the nineteenth century contains reports of several cases in which the fate of the fetus was studied. In these early reports, no radical treatment was employed; consequently, the pregnancy was not interfered with. In a third of the cases reported by Cohnstein, the pregnancy terminated in premature delivery or abortion; in two-thirds of the cases in which the pregnancy was permitted to continue to term, the infants were born dead or died shortly after birth. The experience of Theilhaber and Van der Veer were similar. For many years, however, treatment has not been directed so much at saving the fetus as it has been at controlling the carcinoma. Cesarean section now offers the same excellent chance for a viable fetus as it does in certain other obstetric conditions.

In those cases collected by Strauss, in which an attempt was made to control the lesion by irradiation and at the same time secure a living

child, only 37 per cent of the pregnancies progressed to term and in 18 per cent of these cases children proved to be microcephalic idiots.

*Maternal Prognosis.*—Prior to the end of the last century, the woman with carcinoma of the cervix was almost certainly expected to die. This was true regardless of a complicating pregnancy; only very rarely did the carcinoma respond to local measures. The addition of pregnancy to the disease merely hastened the inevitable end. The immediate mortality was high; 40 per cent to 60 per cent of the mothers failed to survive delivery.

The surgical approach to the disease improved matters considerably. In 24 to 30 per cent of cases in which radical hysterectomy was employed, the patients were alive five years later. By 1910, cesarean section had cut the immediate maternal mortality to 22 per cent. In fifty cases collected by Pankow, the operability rate was 92 per cent and the five-year survival rate was 42 per cent. Of six patients treated at the Stanford University Hospital five have lived five years or more after their dismissal. Two were treated by hysterectomy and the remainder by irradiation.

Many authors feel that the rate of operability is higher in the presence of pregnancy and that the prognosis is no worse when pregnancy is present than it is when pregnancy is not present. It has been a common opinion that young women with cervical carcinoma do less well than do older women, and the experience of Neill tends to support this view. However, Bowing, in a recent review of 1,491 cases of cervical carcinoma, was more encouraging as he found that young women have only a slightly poorer prognosis than do older women. In our series of twenty-six cases, we did not find any definite relationship between the age of the patients and the extension of the lesion or between the age of the patients and the period of survival.

*Family History.*—The family history in this series of cases is most interesting. Seven, or 35 per cent, of the twenty patients who were observed five or more years prior to 1941 gave a family history of carcinoma. Fourteen of the twenty patients are dead; all died of carcinoma except one (Case 11), who died as a result of an accident. All but one of the living patients gave a family history of carcinoma. Since five of the seven patients who gave a family history of carcinoma obtained at least ten-year cures, one might be tempted to offer the hypothesis that such patients were "cancer conscious" and would be likely to seek treatment early in the course of their disease. Investigation showed that this reasoning does not hold true. In one case a large carcinoma of the cervix was discovered on the third post-partum day when an attempt was made to control persistent hemorrhage. In another case, the carcinoma was discovered two months after symptoms developed, but in the remaining cases, symptoms had been present for five to twelve months before the diagnosis was made. In these cases, the patients did

not obtain diagnosis and treatment any earlier than do patients with a completely negative family history and we are at a loss to explain the cause for the more favorable results in cases in which there was a family history of carcinoma.

*Stage of Lesion.*—In five of the seven cases in which the lesion was classified as stage 1\*, the patients were alive when follow-up data were last obtained; however, in three of these cases, less than five years had elapsed since the patients were treated at the clinic. Two, or 50 per cent, of the remaining four patients were alive when the last follow-up data were obtained.

The lesion was classified as stage 2 in nine cases. When the last report was received, five of the nine patients were living. In seven of the nine cases, ten or more years had elapsed since the patients were treated at the clinic and three of the seven patients, or 43 per cent, were alive.

The lesion was classified as stage 3 in six cases. Only one, or 17 per cent, of the six patients is known to be alive. In this case, eleven years have elapsed since the patient was treated at the clinic. There was no evidence of recurrence of the lesion when the last follow-up data were obtained.

As might be expected, in *all* of the four cases in which the lesion was classified as stage 4 the patients died of the disease or of incidental complications.

*Grade of Malignancy.*—The effect of the grade of malignancy and of the type of lesion will be considered in a subsequent paper on this subject.

*Duration of Symptoms.*—Although the number of cases in this series is too small to justify definite conclusions, it would appear that better results will be obtained when the lesion is recognized in seven months or less after the onset of symptoms. In the twenty cases in which the patients were followed more than five years, good results were obtained in 38 per cent of cases in which the tumor was recognized within nine months after the onset of symptoms but in only 14 per cent of cases in which the symptoms were of longer duration.

Curiously, however, five patients who had had symptoms for a year or more all lived at least one year after they were treated at the clinic. One lived one year; one, twenty-two months; one, two years; one, six years, and one is still living after ten years. In contrast, a group of ten patients (not including patients classified as "cured") who had had symptoms for less than one year fared less well; one lived fifteen months but the remaining nine died in ten months or less from the time the lesion was discovered. It would appear that if a good result is not obtained the patient who has had symptoms of carcinoma for more than one year before the diagnosis is made will survive longer than one who has had symptoms for a shorter period.

\*International classification.

*Type of Therapy.*—It is difficult to draw definite conclusions as to the type of therapy that produces the best results, since this series of cases is relatively small and the different types of therapy have not been used in comparable cases. The findings, however, justify certain statements. Porro cesarean section has produced poor results for the mother in all cases in which it was employed. In cases in which the lesion was operable, the best results were obtained by total hysterectomy. In four of seven cases in which this operation was performed, the patients have lived ten or more years after the operation. In one of three cases in which vaginal hysterectomy was performed, the patient is living ten years after operation.

It is difficult to state how much the prognosis is improved by subsequent use of irradiation therapy. This type of therapy is not necessarily essential since one patient, who is alive twenty-three years after abdominal hysterectomy, was not given supplementary irradiation. In only two instances was irradiation used as the sole treatment in cases in which the lesion might be classified as operable; in both of these cases the patients died of extension of the lesion. In contrast, in a case in which the lesion was stage 3 and the prognosis apparently hopeless, the response to irradiation was excellent. In this case, the patient is free of recurrence of the lesion ten years after treatment.

### Summary

A study of 3,570 cases of carcinoma of the cervix observed at the Mayo Clinic in approximately thirty-two years revealed that pregnancy was present in twenty-six, or 0.7 per cent, of these cases when the carcinoma was found. This figure does not necessarily indicate the true incidence of carcinoma of the cervix coincident with pregnancy as all of the 3,570 patients came to the clinic because of carcinoma of the cervix and not because of pregnancy. In the same period covered by this study, 8,500 pregnant women were observed at the clinic.

The average age of the patients in the twenty-six cases in which carcinoma of the cervix was coincident with pregnancy was 32 years. The youngest patient was twenty-five years of age and the oldest patient was forty-one years of age. The prognosis was no worse in the case of young patients than it was in cases in which the patients were older.

The average number of previous pregnancies was 6 and the average number of children was 4. The number of pregnancies apparently did not affect the prognosis. In cases in which the carcinoma was diagnosed in the later months of pregnancy, the lesion usually was well advanced and the prognosis was poor.

Pregnancy may occur after carcinoma of the cervix has developed. A family history of carcinoma was elicited in seven, or 35 per cent,

of the twenty cases which were observed five or more years prior to 1941. The prognosis in these seven cases was better than the prognosis in the remaining cases.

Bleeding was the initial symptom in twenty-three, or 88.5 per cent, of the cases. In 25 per cent of the cases, the patients did not realize that they were pregnant when the diagnosis was made.

No definite conclusions can be drawn concerning the relative value of irradiation therapy; however, it appears that operation is preferable in cases in which the lesion is operable and that supplementary irradiation increases the percentage of good results. This is in contrast to the relative value of irradiation therapy and hysterectomy in cases of carcinoma of the cervix in which the patients are not pregnant.

We are in general agreement with Strauss concerning treatment of carcinoma of the cervix coincident with pregnancy. If the extent of the lesion permits operation and if the fetus is not yet viable, total hysterectomy is followed by irradiation; if the lesion is operable and the fetus is viable, cesarean section is followed by panhysterectomy and postoperative irradiation.

In cases in which the lesion is nonoperable and the fetus is viable, cesarean section is followed by irradiation; in cases in which the lesion is nonoperable and the fetus is not yet viable, sufficient irradiation is employed to treat the lesion; incidentally, abortion occurs.

In cases in which the lesion is operable, total abdominal hysterectomy has produced the best results. In 57 per cent of the cases in which this procedure was employed, the patients were free of recurrence five years after the operation.

In this series of cases of carcinoma of the cervix coincident with pregnancy, many of which were observed before the present methods of treatment were developed, the prognosis appeared to be at least as favorable as the prognosis of carcinoma of cervix that is not associated with pregnancy. Of the twenty patients who were followed, 30 per cent were free of recurrence five or more years after they had been treated at the clinic.

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## PELVIC INFLAMMATORY DISEASE OF SPECIFIC ORIGIN

### A Comparative Study of Two Series of Cases From the Charity Hospital of Louisiana at New Orleans, With Special Reference to Recent Therapeutic Improvements and Their Effect on the Mortality

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RECENTLY I found in the files of my brother, the late Dr. C. Jeff Miller, some of the tabulated data used as the basis of the studies which he had published in 1927 and 1928<sup>1, 2</sup> on specific salpingitis and the allied conditions loosely classified as pelvic inflammatory disease. The files also contained the abstracts of material from periodicals and other literature used as background for these studies. Although some detailed data which would have been useful are missing, enough material was found to make me believe that a comparative analysis of the same diseases at this time would be of interest, particularly in respect to the effect upon the mortality of the therapeutic changes introduced in more than fifteen years which have elapsed since the original studies were published. A survey of the gynecologic literature for the past five years has confirmed my impression that only a rather limited number of surveys of pelvic inflammatory disease have recently been published, although to gynecologists who practice in areas where there are large Negro populations only uterine fibroids present problems of equal importance.

C. J. Miller's studies were based on (1) a gross analysis of the 6,184 cases of pelvic inflammatory disease treated in the Charity Hospital of Louisiana at New Orleans during the 10-year period ending January 1, 1926 (Table I), and (2) a detailed analysis of 300 recent consecutive surgical cases from the same institution, and of 300 similar cases from Touro Infirmary in the same city. I have confined my own studies (Table I) to the New Orleans Charity Hospital, where, generally speaking, specific pelvic inflammatory disease is seen in far greater frequency and usually in far graver aspects than at private institutions. They include (1) a gross analysis of 3,072 cases of salpingitis and allied conditions treated over the three-year period ending September 30, 1942; (2) a detailed analysis of the 16 surgical and 14 non-surgical deaths which occurred during the same period; and (3) a detailed analysis of 500 nonfatal surgical cases treated during the same period, the object of the latter analysis being chiefly a determination of recent trends of treatment.

#### General Considerations

Of the specific origin of most cases of pelvic inflammatory disease at the New Orleans Charity Hospital, the gynecologists who treat them



have very little doubt. When acute primary infections of the lower genital tract are seen promptly, which they seldom are, even in white women of the class treated at this institution, bacteriologic proof of gonorrheal disease is forthcoming in a large number of cases. When the infection has reached the tubes, bacteriologic proof of a specific origin is usually lacking, partly because laboratory examinations are not performed as often as they should be, and partly because even cultural methods, though superior to smears,<sup>3, 4</sup> are themselves unsatisfactory in most cases. Lewis,<sup>5</sup> for instance, was able to diagnose only six of 80 cases of pelvic inflammatory disease at the New Haven Hospital by cultural methods, and Mahoney's incidence of successful cultures (cited by Lewis) in 1,598 prostitutes was only 21 per cent, which approximates the percentage of success in the cases at Charity Hospital in which cultures were made. Be this as it may, the disease is overwhelmingly more frequent in Negro women (Table II), and, as C. J. Miller pointed out, when pelvic pathology in women of this race at this institution is interpreted in the light of the findings in the Negro male population, it can obviously be attributed to specific infection in all but a small proportion of cases.

The history of pelvic inflammatory disease is usually typical, particularly in young women, but in women of the social level treated at Charity Hospital, either because of the patients' ignorance or because

TABLE I. TWO SERIES OF CASES OF PELVIC INFLAMMATORY DISEASE AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	C. J. MILLER*	H. E. MILLER
	1927	1943
Total cases	6,184	3,072
Deaths	153	30
Per cent	2.5	1.0
Surgical cases		2,128
Deaths		16
Per cent		0.75
Nonsurgical cases		944
Deaths		14
Per cent		1.87

\*The breakdown for this series into surgical and nonsurgical cases is not available. The mortality is a case mortality. In the period covered by the figures the unit system of admission was not in effect, and readmissions were counted as if they were new cases. The actual patient mortality would therefore be higher than 2.5 per cent, and the difference between this mortality and the less than 1 per cent patient mortality reported for the recent period is actually greater than is apparent.

TABLE II. COMPARATIVE WHITE AND NEGRO STATISTICS OF PELVIC INFLAMMATORY DISEASE IN A RECENT THREE-YEAR PERIOD AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	CASES	DEATHS	PER CENT
Total cases	3,072	30	0.1
White	733	6	0.82
Negro	2,339	24	0.1
Surgical	2,128	16	0.75
White	432	3	0.69
Negro	1,696	13	0.77
Nonsurgical	944	14	1.87
White	301	3	1.0
Negro	643	11	1.7

of their deliberate intent to deceive, their stories are frequently confusing. Thus in the 500 cases recently studied in detail, although 25 women classified themselves as single, eight of them were later found to have had abortions or full-term pregnancies or both, and pelvic examination in the remaining cases vitiated the professions of virginity. In addition, many of the 475 women who classified themselves as married admitted promiscuous sex relations.

A definite history of recurrent attacks of pelvic disease, which occasionally were frankly stated to be due to "pus tubes," was obtained in 64 cases, and 33 other patients had been repeatedly treated in the hospital during recurrent acute attacks or had been discharged to cool at home in preparation for operation. Unilateral salpingectomy had been previously performed in 28 other cases, colpotomy (in one instance on two occasions) in three cases, and abdominal drainage and drainage of a Bartholin gland abscess in one case each. Laboratory examination of the excised tubes revealed salpingitis isthmica nodosa in 63 cases, and more careful examination would probably have materially increased the percentage. Schenken and Burns<sup>6</sup> have recently studied this condition at the New Orleans Charity Hospital and have again called attention to the association between it and gonorrheal infection.

In the 500 cases recently studied at Charity Hospital exact data as to the onset of the original infection could be secured in less than 10 per cent, and the apparent time of extension to the tubes could be secured in only 31 instances. The upward extension was precipitated by abortion (in several instances criminal and in one repeatedly criminal) in nine cases, by delivery in 11, by the sex act in five, and by a menstrual period or by operation on the cervix in three each. In one of the fatal cases the tubal disease clearly dated from coitization of the cervix.

It is hard to explain, although the fact is well known, why some women with almost completely frozen pelves are in relatively good health, while others, with far less demonstrable pathology, are for all practical purposes complete invalids. Negro women, who as a group present far more serious pelvic changes than white women, are inclined to be much less affected by them and frequently ignore their illness until pain becomes severe or until they are incapacitated by other symptoms. These differences in reaction can perhaps be attributed to racial differences in the threshold of pain. Whatever the reason, they are of great practical importance: In the group of fatal cases one Negro woman remained at home without treatment until she was actually moribund, while three others died so soon after admission to the hospital as to make all treatment futile. Incidentally, the tendency to take purgatives for abdominal pain was, as usual, evident in both Negro and white women.

Since a vaginal discharge is a prominent feature of pelvic inflammatory disease, it is surprising to find it complained of by only 38.6 per

cent of the 500 patients, which is about the same proportion reported in Miller's earlier series. These low percentages are corroborated by Guerriero and Arnell,<sup>7</sup> who found that less than a third of 433 pregnant women with nonbloody vaginal discharges studied at the New Orleans Charity Hospital considered this symptom worth mentioning in their histories, or actually denied its existence, although, as in these two series, a vaginal discharge was actually and profusely present in a much larger number on pelvic examination.

Although diagnosis was not difficult in most of the 500 cases emergency operations were performed on the mistaken diagnosis of acute appendicitis in eight instances. Boyce<sup>8</sup> has recently reported 60 other "unnecessary" emergencies of the same kind, and I am completely in accord with his conclusion that such operations are usually justified. In contrast to the absence of mortality in these 60 cases, he cites, from other studies of his own, three deaths in 46 cases of acute appendicitis in which operation was postponed for varying intervals on a mistaken diagnosis of pelvic disease, as well as seven deaths from acute appendicitis in which operation was not performed at all on the same mistaken diagnosis. I am also in agreement with Boyce's warning that if the abdomen should be opened on an apparently mistaken diagnosis and pelvic inflammatory disease should be found, the surgeon should usually refrain from pelvic surgery, though, regardless of the state of the pelvis, he should search for and thoroughly examine the appendix, to be certain that it is not also the site of a primary pathologic process.

### Nonsurgical and Adjunct Therapy

Results at the New Orleans Charity Hospital support Lewis<sup>9</sup> discouraging statement that all forms of therapy in pelvic disease have to date been remarkably unsuccessful and amount to little more than watchful waiting, with surgical interference when necessary. They also support his statement that in the past, therapeutic methods have been credited with curing patients who really cured themselves and who frequently recovered in spite of rather than because of the treatment they had received. For my own part, I do not exclude chemotherapy when I say that except for general measures, which must frequently be followed by surgery, no treatment of specific pelvic inflammatory disease has to date given even approximately satisfactory results. I would go even further and say that the general measures usually employed with most other forms of therapy are probably more responsible than any special measures which may be employed for such results as are achieved.

Diathermy (15 cases), [the Elliott treatment (seven cases) and protein therapy (five cases)] were used in the recent series studied at Charity Hospital, with no notable and no permanent results from the standpoint of either clinical or anatomic improvement. My results in private practice with all three methods have been equally poor. G. A.

Williams,<sup>10</sup> whose statistics, because they relate to Negroes, are peculiarly comparable to my own, states that a prolonged trial of protein therapy at Grady Hospital in Atlanta has indicated its uselessness in this race. He also sets forth the shortcomings of the Elliott treatment in a public institution. Very significant is the fact that of 369 women treated by this method at Grady Hospital, approximately 40 per cent either disappeared from observation or failed to cooperate long enough to permit adequate treatment. Of those observed from four to 26 months—the former period being much too brief to warrant statements as to end results—1.9 per cent died, 15.8 per cent showed no improvement, and only 28.7 per cent could be regarded as cured. These results, Williams points out, are by no means as favorable as those reported by other authors in white or white and colored patients combined. As might have been expected, the best results were obtained in recent acute cases and the least good in chronic cases with frozen pelves.

*Chemotherapy.*—The statement that I do not regard the greatly improved mortality of pelvic disease at the New Orleans Charity Hospital in recent years (Table I) as due to chemotherapy will occasion no surprise to those who have used the sulfonamides in this condition. Goff's<sup>11</sup> statement that the results of chemotherapy in female gonorrheal infections are proving more and more disappointing has found many echoes in addition to my own. Barrows and Labate,<sup>12</sup> for instance, whose studies were made with smears and not with cultural methods, found that primary attacks of less than five days' duration were apparently cured after a week of chemotherapy in 70 per cent of mild and 66 per cent of moderate cases, but that cases of longer duration, whether mild or severe, and recurrent cases showed no adequate response. J. T. Williams,<sup>13</sup> after reviewing the literature, which does not contain a great deal on chemotherapy in salpingitis, concluded that the results are not likely to be good after the initial attack or after pelvic masses have formed; most cases at Charity Hospital fall into these two groups. In a treated series of cases, contrasted with a control series similarly managed except for the omission of chemotherapy, Williams found no special differences in regard to improvement of symptoms, duration of fever, and other clinical phenomena, while the incidence of surgery was substantially the same in both.

An evaluation of chemotherapy in the Charity Hospital series presents certain difficulties. In many cases it was not indicated. In many instances it was impossible to determine whether the drugs were used tentatively (a policy which Stokes<sup>14</sup> has warned against on the ground that it may establish a presumption of malpractice) or as a deliberate phase of the adjunct treatment. All routes of administration were used, as were most of the suggested dosages, and neoprontosil, sulfanilamide, sulfapyridine and sulfathiazole were all employed, sometimes in the same case.

Chemotherapy does not seem to have been employed in any instances in the primary infection of the lower pelvis, chiefly because not more than two or three patients, at the most, seem to have received treatment at that time. Only 20 patients, in all of whom the results were poor, stated that they had taken sulfonamides in some form before their admission to the hospital with pelvic inflammatory disease. I have no doubt, judging by my own experience in private practice, that many other patients were thus treated and merely did not know what drugs they were receiving, but it was naturally impossible to identify this group.

Chemotherapy was used either in an endeavor to avoid surgery or as a preoperative measure to control infection in 21 of the 238 patients who entered the hospital with some degree of fever. All of the cases were of long standing and in all the results were poor, as might have been expected. Experience has shown that chemotherapy does not give good results in encapsulated appendiceal abscess, and there is no reason to anticipate better results when chemotherapy is practiced after an inflammatory reaction has resulted in closure of the tubes, accumulation of exudates, development of tuboovarian abscesses, and extensive structural alterations. These changes, as already pointed out, are seen in a large majority of cases of pelvic disease at Charity Hospital, particularly in Negro women, most of whom present recurrent disease, and it is unreasonable to expect chemotherapy or any other form of nonsurgical treatment to effect the miracle of an anatomic cure. Furthermore, if Barrows and Labate's<sup>12</sup> criterion be used, that the patient must be treated within five days of her primary attack, good results could not have been expected in most cases in this series, since only 30 of the 500 women were seen within the first week of their illness.

Although I have no statistics on this point, I think it well to emphasize, in view of the carelessness with which the sulfa drugs are sometimes used, that early assumption of cure, unconfirmed by cultural methods, is both misleading and dangerous. This is particularly true of Negro women, whose mode of living frequently violates all the laws of sex hygiene. Lewis<sup>9</sup> endeavors to meet this risk by issuing prescriptions for only 48 hours at a time, but the defect of this precaution, which requires attendance at the clinic every third day, is that it breaks the continuity of bed rest, which personally I regard as the most important phase of treatment.

According to the records, sulfanilamide was used in the peritoneal cavity and in the layers of the wound in 35 of the 469 cases in which laparotomy was performed. Again I suspect that the number was much larger and that the operators merely failed to make their operative notes complete. An estimation of the exact results is impossible, but it is fair to say, on the basis of my own experience, that many potential infections are averted by this method and that many actual

infections are controlled and rendered less virulent. It may be significant, furthermore, that this method was not used in any of the 16 fatal surgical cases, in seven of which peritonitis was the cause of death and in one of which a massive wound infection played an important part in the fatal outcome.

Chemotherapy, chiefly by the oral route, was used as a postoperative measure in 99 cases. In 37 the indication was urinary tract infection, usually limited to the bladder, and the results in all cases were prompt and good. In some 10 cases the indication for chemotherapy was not clear and the method seems to have been used only tentatively. In the remaining cases peritonitis was either present at operation or its development seemed likely. Though improvement eventually occurred in all of these cases, it was considerably less prompt than when urinary tract infection was the indication for chemotherapy, and other measures, such as infusion, transfusion, and intestinal decompression, should probably be credited with a large part of the final good results: In a few instances long continued pyrexia terminated within a day or two after withdrawal of the sulfonamide, and was clearly a reaction to the drug.

The sulfonamides, chiefly in the form of sulfathiazole, were used in every one of the 14 fatal nonsurgical cases, in several of which, however, death occurred too promptly for any form of therapy to be effective. They were used both before and after operation in all the fatal cases (11) in which infection was responsible for the fatality. They do not seem to have affected the outcome even transiently in any case in either of these groups, and in one or two of the nonsurgical cases they apparently led to the complacent belief that other measures might safely be omitted; at any rate, such measures were instituted late. Two instances of dermatitis and three of jaundice in the fatal cases and one instance of jaundice in a nonfatal case are evidence that this is not a harmless form of therapy, especially in patients whose initial general condition is poor.

*General Measures.*—I have examined with interest the methods of nonsurgical and adjunct therapy employed in C. J. Miller's<sup>1, 2</sup> reported cases and advocated in the material from the literature which he used as background. They consisted chiefly of complete bed rest, sometimes in the Fowler position; the local application of icecaps or heat; a liquid or semiliquid diet; measures for the control of pyrexia; regulation of the bowel function (although some writers advised the daily use of a saline purgative, Miller considered anything more forceful than a low enema to be unnecessary if not harmful); and hot or cold douches for the control of annoying discharges. Miller considered the local application of iodine or other antiseptics to be futile if not dangerous, and he warned that pelvic examinations should be performed very gently and only as necessary to follow the progress of the disease.

General measures which put the pelvic structures at absolute rest are still the basis of all successful nonsurgical treatment of pelvic inflammatory disease, but the adjunct treatment of the condition is now very different. Very striking in Miller's reported cases and in the current literature which he abstracted is the absence of emphasis on fluid therapy and blood transfusion. In his reported cases fluids were administered parenterally only to the occasional patient and usually by proctoclysis and hypodermoclysis. Transfusion seems to have been chiefly an ante-mortem measure. In some papers which he abstracted fluid therapy is not even mentioned, and transfusion is suggested only by Doherty,<sup>15</sup> an advocate of immediate radical operation for acute salpingitis, who proposed it only for "septic cases."

In the period between 1927 and 1943, there have been important changes in the concept of the fluid balance of the body, infusion has become a part of the surgical routine, and massive transfusion has been developed. A comparative analysis of the recent and the original series of cases leaves no doubt that it is the careful application of these advances, plus more adequate preoperative and postoperative care, especially with respect to replacement of body fluids and maintenance of the fluid balance, which accounts for the chief reduction in the mortality of specific inflammatory disease in recent years at the New Orleans Charity Hospital.

In the recent series even moderately dehydrated patients were infused one or more times before operation if the fluid balance could not be satisfactorily maintained by oral intake, and more than 25 per cent (131) were infused after operation. The more seriously ill patients were thus treated for periods of time which sometimes exceeded 21 days. Forty-one patients were transfused one or more times before operation and 42 were transfused after operation. Infusions and transfusions were also used freely in the fatal cases. One patient in the latter group had 3,600 c.c. of blood before operation, and only two patients were not transfused at all. In one instance the omission seems to have been due to poor judgment. In the other, no donors could be secured, a difficulty which the recent establishment of a blood and plasma bank at Charity Hospital should obviate for the future.

Other adjunct measures, most of them of recent development, were also profitably employed both before and after operation in the recent series. Anemia not serious enough to require transfusion was combated by liver extract and preparations of iron. Suspected or proved vitamin deficiencies were corrected by appropriate measures, as was hypoproteinemia. The rectal tube and prostigmine and similar preparations were used before and after operation as indicated, and constant intestinal decompression was instituted if these simpler measures were not immediately successful. Changes of position and inhalations of carbon dioxide and of oxygen were used as prophylaxis against the development of pulmonary complications.

### Postoperative Complications

As a result of these measures, although the first few days after operation were critical in perhaps 40 of the 500 surgical cases, and although 16 patients had prolonged and stormy convalescences, postoperative complications were neither frequent nor serious, except for wound infection. This complication developed in 49 cases, in 12 of which incision and drainage were necessary. Delayed healing was observed in three cases, in one of which a frank hernia developed, but evisceration did not occur in any instance in the nonfatal cases. For the almost 10 per cent incidence of wound infection I have no explanation.

Ileus was rarely observed, and peritonitis developed after operation in only one case in which it had not been present before operation. Postoperative urinary tract infections were serious in only 11 of the 37 cases in which they developed, and pneumonitis and other respiratory tract infections occurred in only 10 cases. Hemorrhage and thrombophlebitis occurred in two cases each, and jaundice and hepatomegaly were observed in one case each, in both instances following chemotherapy.

The incidence of complications in the recent series is several times smaller and the complications were generally much less serious than in C. J. Miller's group. The difference, I am sure, can be attributed to improved preoperative and postoperative therapy. It was definitely not due to the better condition of the patients, for many in the recent series presented serious complications, aside from their pelvic disease. One hundred twelve had hypertensive or cardiac disease, usually improved, incidentally, by bed rest and medical measures instituted before operation. Forty-five had been treated for syphilis, usually incompletely because of their own lapses, and the blood serologic test was presently positive in 119 cases; one patient had tabes dorsalis. Seventeen patients presented hepatomegaly, though tests of liver function were unfortunately not carried out in any case. Six had pyelitis and three nephritis, and some degree of cystitis was initially present in more than a third of the 500 patients; usually these infections responded promptly to simple measures, but when they did not, chemotherapy was employed. Other associated conditions included umbilical hernia (15 cases), ventral hernia (three cases), and diastasis recti (eight cases), lymphogranuloma inguinale (two cases), and pellagra, typhoid fever, and epilepsy (one case each). Sixty-seven patients were obese, many weighing 200 pounds and more. Four were cachectic and three others greatly dehydrated from vomiting and diarrhea. In 103 cases the hemoglobin on admission to the hospital ranged downward from 70 to 28 per cent, and in 62 cases the red blood cell count ranged downward from 3,500,000 to 1,500,000 per cu. mm. Forty-one patients were admitted so gravely ill that long preparation for operation was necessary.



C. J. Miller called special attention to the fact that in the 600 cases he reported, 72 per cent of the postoperative complications, 72 per cent of the postoperative temperature elevations over  $101^{\circ}\text{F}$ ., and 16 of the 18 deaths occurred in the patients who had not been properly cooled before operation according to Simpson's<sup>15</sup> criteria. In the 500 cases now reported, 34.4 per cent (172) were also operated on without full adherence to these criteria, this group including, however, the cases in which the ovary was implicated and in which temperature elevations frequently continue until surgery is carried out. On the whole, although the violations of Simpson's criteria were far less marked than in the earlier series, the results of the violations were much the same. Eighty-one per cent (189) of the postoperative temperature elevations over  $101^{\circ}\text{F}$ ., and 70 per cent of complications occurred in this group. Of the 75 patients kept in the hospital longer than 10 days (the present desired maximum under crowded conditions and necessary economy), 54 per cent had been incompletely cooled, and 44 per cent of the patients discharged with some degree of fever had also been incompletely cooled. In the fatal surgical cases, however, the patients were in such condition in only three or four cases, at most, as to make the outcome anything but doubtful, regardless of how long they had been cooled.

*Rupture of Pelvic Masses.*—Until I had completed this study I should have subscribed to the general idea that rupture of pelvic masses is an unlikely accident in pelvic inflammatory disease. I have necessarily changed my mind. Of the 41 tuboovarian masses included in the 500 nonfatal surgical cases, two had ruptured before operation and the same accident had occurred in three of the 16 fatal surgical cases. There were also three instances of rupture, all proved by autopsy, in the 14 fatal nonsurgical cases. In one instance, the accident followed so closely upon bimanual examination as to suggest a possible cause and effect relationship. I have already located nine other instances, seven of them proved by autopsy, of this supposedly infrequent accident in a study I am now making of gynecologic deaths at the New Orleans Charity Hospital over a recent period. The tabulated data I have available from C. J. Miller's study do not permit a determination of how many of the five instances of rupture in his 600 cases terminated fatally.

### Surgical Therapy

A few comments are necessary on the various surgical procedures carried out in this series (Table III). In two of the six cases in which surgery was limited to simple drainage of the abdominal cavity, colpotomy had previously been carried out. The eight cases in which only appendectomy was performed have already been discussed. In the three cases in which only exploration was performed it was the surgeon's opinion that any attempt to remove the infected pelvic struc-

tures would be attended with too much risk because of the involvement of the intestines in the pelvic adhesions. In such cases the corneal resection devised by Falk<sup>17</sup> might be of value, though I have had no personal experience with it. The basis of the operation is the pathologic fact that recurrent salpingitis is caused by repeated upward extension of infection along the endometrium, and its rationale is the interruption of this epithelial continuity. Falk's excellent results from the Harlem Hospital, where the material is rather similar to that of the New Orleans Charity Hospital, include 78 per cent of anatomic, 85.5 per cent of clinical, and 97.8 per cent of economic cures, the latter being a consideration of extreme importance in women of these social levels.

TABLE III. COMPARATIVE SURGICAL PROCEDURES IN TWO SERIES OF CASES OF PELVIC INFLAMMATORY DISEASE AT CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

	C. J. MILLER <sup>*</sup> 1927	H. E. MILLER 1943
Total cases	600	500
Bilateral salpingectomy	436	425
with hysterectomy		391
with bilateral oophorectomy		364
with unilateral oophorectomy		24
Unilateral salpingectomy	154	34
with hysterectomy		31
with oophorectomy		10
Drainage only	3	6
Plastic on tubes	17	3
Exploration only		3
Exploration and appendectomy		8
Colpotomy		21
†Appendectomy also	343	273
†Drainage also	78	10

\*All the details of the operations in this series are not available, but it is known that hysterectomy was done in 99 cases.

†These figures are overlapping.

Specific pelvic disease is one of the few conditions in gynecologic practice in which conservative surgery is frequently ill advised. The tendency in this disease is for unilateral infection to become bilateral, and the chances of functional recovery of affected tubes are notably poor. In the 500 cases I am reporting, 21 patients, 4.2 per cent, had already been submitted to previous conservative surgery (exclusive of the group in whom only exploration or only colpotomy had been carried out), as had 3 per cent of the patients in C. J. Miller's series. The proportion of previous conservative surgery was 6.3 per cent in 94 cases reported by Craig and Kraff,<sup>18</sup> and it was 24 per cent in Whitehouse's<sup>19</sup> series.

In C. J. Miller's series the incidence of bilateral salpingectomy (Table III) was 72.6 per cent; in my own series it had risen to 80.5 per cent. I seriously question the wisdom of, or the justification for, the plastic operations on the tube, in one instance combined with resection of the ovary, done on three Negro women in my own series, but the figure is an improvement over the earlier series, in which resection of, or

plastic operations on the tube were done in 17 instances and resection of the ovary or ovarian grafting was done in 34 cases. In twenty-five years' experience at the New Orleans Charity Hospital I have never personally seen a case in which I regarded plastic surgery on the tubes as justified.

The difference in the incidence of hysterectomy in my own and in the earlier series is striking (Table III), 80 per cent (401 cases) versus 16.5 per cent (99 cases). The tendency toward more radical surgery is entirely justified. When the tubes have been removed the uterus is always a useless and frequently a troublesome organ. This is a serious consideration in women whose livelihood depends upon their own efforts, quite aside from the risk of a second operation. That this risk is real is shown by McDermott's<sup>20</sup> figures: In a series of 839 hysterectomies, 11 per cent of the patients had previously been submitted to unilateral or bilateral salpingectomy.

Since the tendency at the New Orleans Charity Hospital is more and more to perform total hysterectomy in the absence of indications to the contrary, the fact that approximately 37 per cent (147) of the 391 hysterectomies were supravaginal may be interpreted as indicative of the serious condition of many of these patients. Of the 10 hysterectomies performed in the 16 fatal surgical cases, however, only three were supravaginal, and in view of the generally poor status of these patients it might have been the part of wisdom to use the incomplete procedure more often. When performed with due regard to contraindications, the complete operation, in spite of an impression to the contrary, does not increase the mortality, and sometimes is attended with fewer deaths. In my own study with Prejean<sup>21</sup> from the New Orleans Charity Hospital the mortality for complete hysterectomy was 1.33 per cent, against 2.75 per cent for the supravaginal operation. An additional advantage of the complete operation is the absolute protection it furnishes against the later development of cervical malignancy. In one of the cases in the present series the patient returned in four months with carcinoma of the cervix so far advanced that it evidently had been present when the supravaginal hysterectomy was done as part of the operation for pelvic disease. I might add that Prejean and I found carcinoma of the cervix as an entirely unexpected finding in 12 of the 255 complete hysterectomies which we reported in 1941.

Appendectomy had previously been performed in 30 of the 500 cases, and was carried out at operation in 273 of the remaining 449 laparotomies (63 per cent), as compared with an incidence, so far as I can calculate from the data available, of about 56 per cent in the earlier series. It is generally routine in gynecologic surgery at the New Orleans Charity Hospital when it does not add materially to the risk or prolong the operation unduly. Under the most favorable circumstances, however, it carries a small additional risk, and the fact that

it was not done in so many possible cases can be construed as evidence of surgical prudence. Appendectomy was performed in three of the fatal surgical cases, and in one, at least, seems to have been an error of judgment. Medical consultants had warned that the patient was an extremely poor risk because of her cardiac state.

The approximately 2 per cent incidence of drainage in the series I am reporting (10 of 473 possible cases) is to be compared with the 13 per cent incidence reported by C. J. Miller (78 of 597 cases). The indications in the second series were chiefly oozing and uncertainty as to hemostasis. Even when tuboovarian abscesses were ruptured in the course of removal, as happened in 19 instances, it was seldom employed. The present plan of drainage only on strict indications has played a definite part, I am sure, in the improved mortality of surgical pelvic inflammatory disease at the New Orleans Charity Hospital, and I am equally sure that it has reduced the number of postoperative abdominal complications.

As in all similar institutions, the surgery at Charity Hospital continues to be done, as it has always been done, by surgeons of all grades of training and experience. Since C. J. Miller's report was made, however, a resident system has been instituted, and a large proportion of the surgery in the period covered by my report was done by these young men. The lowered mortality is a credit to them and to their training, and the great improvement in preoperative and postoperative care must in all fairness be attributed to their conscientious work.

### Pelvic Inflammatory Disease in Negro Women

It is unrealistic to discuss gynecologic statistics from the New Orleans Charity Hospital without calling attention to the high incidence of certain diseases, especially pelvic inflammatory disease and uterine fibroids, in this race. More than 76 per cent of the total incidence of specific pelvic disease over the three-year period covered by this report (Table II) occurred in Negro women, as did more than 79 per cent of the surgical salpingitis, and 80 per cent of the total mortality. In evaluating these proportions, the hospital ratio of admissions, which averages 55 white to 45 Negro patients, year in and year out, should be borne in mind.

In the 500 cases studied in detail, 305 of the 430 Negro women presented uterine fibroids, usually very large, as compared to 12 of 70 white women, in whom the growths were uniformly small. This association is well known to surgeons who operate on Negro women. Torpin and his associates,<sup>22</sup> for instance, found a 54 per cent incidence of pelvic inflammatory disease in Negro women operated on for fibroids, and a 40 per cent incidence of fibroids in Negro women operated on for pelvic inflammatory disease.

Everything that Miller wrote sixteen years ago about the treatment of pelvic inflammatory disease in Negro women still holds true. She

is difficult to separate from her infected partner, and she seldom co-operates fully in attempts at prolonged physical and sexual rest. Whether the cooling period is spent in the hospital or at home, there are frequent defections, and even when the prescription is obeyed, the disease tends toward chronicity and frequent exacerbations. Recovery under nonsurgical therapy is not the rule. Surgical procedures are necessary in a large proportion of all cases and are frequently very difficult. Pathologic changes include tuboovarian abscess, pyosalpinx, and cul-de-sac abscesses, and the pelvic viscera may be so glued together that their identification, let alone their separation, sometimes seems impossible, as indeed it was so regarded in at least three cases in my own series. When all the facts are taken into consideration, the mortality is low enough to warrant the postulate that Negro women either have a higher degree of resistance to infection than white women, or that they develop some special immunity to the gonococcus. It should be added that the hygiene of the Negro home is frequently bad, and that the woman with a gonorrheal infection is likely to infect other members of her family while her disease is proceeding on its upward course.

### Summary and Conclusions

1. A study of specific pelvic inflammatory disease at Charity Hospital of Louisiana at New Orleans shows that the over-all mortality in a series of 6,184 cases reported in 1927 and 1928 was 2.5 per cent, as compared with a mortality of slightly less than 1 per cent in 3,072 cases treated at the same institution over a recent approximately three-year period and reported herewith.

2. Pelvic inflammatory disease in Negro women is more frequent than in white women, is much more frequently associated with fibroids, and as a result of neglect is often much more serious.

3. Rupture of tuboovarian masses, although generally believed to be unusual, was observed in eight cases in this study, in six of which it was fatal.

4. Acute appendicitis furnishes the chief difficulty in differential diagnosis, and statistics show that exploration is justified if the confusion cannot be cleared up promptly. Bacteriologic diagnosis, whether by smear or culture, is highly unsatisfactory.

5. Except for general measures, no treatment of pelvic disease gives even approximately satisfactory results. Chemotherapy is disappointing in infections above the external cervical os, but is a useful adjunct measure in properly selected cases, though it is by no means free from risk.

6. Surgery is ultimately necessary in a large proportion of cases of recurrent salpingitis, particularly in public institutions with a large number of Negro patients. Conservative surgery must frequently be followed by secondary surgery, and plastic operations on the tubes

have little to commend them, especially in women of the poorer classes. Drainage should be used with discretion, and appendectomy should be omitted in poor risk cases and in those in which operation has been unduly prolonged.

7. An analysis of 500 recent surgical cases at Charity Hospital, compared with an analysis of 600 surgical cases from this institution and from Touro Infirmary reported in 1927 and 1928, shows that the recent improvement in the mortality of pelvic inflammatory disease can be attributed to: the free use of fluids before and after operation, especially the parenteral administration of fluids; the free use of transfusion; the institution of measures to correct mild degrees of anemia and vitamin and protein deficiencies; the prevention of ileus by the prompt use of intestinal decompression and other measures; the prevention of pulmonary complications by various prophylactic measures; the employment of drainage only on strict indications; the performance of supravaginal rather than complete hysterectomy in poor risk cases; the omission of appendectomy in all but good risk cases. Chemotherapy played only a minor part in the improved results and was not curative in any case, but was effective as an adjunct form of treatment in properly selected cases. The basic reason for the improvement in the preoperative and postoperative care, which in turn was the basis of the improvement in the mortality, was the institution of a resident system in the hospital.

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# IODINE VAPOR TECHNIQUE VERSUS CARBOLFUCHSIN STAIN FOR VAGINAL SMEARS

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THE iodine vapor staining of vaginal smears, as described by Mack,<sup>1-4</sup> has proved to be a quick and simple quantitative test for cellular glycogen. From older and more difficult techniques it has appeared that the glycogen content of the vaginal mucosa cells is an indication, at least in a general way, of bodily ovarian or estrogenic hormone activity. As a consequence, the newer method, being easy and rapid, may be found after further study to have considerable practical application. As one test of its accuracy in reflecting ovarian hormone activity, a comparison was made of daily vaginal smears stained by iodine vapor with duplicates prepared by one of the older methods which show variations in grading according to cellular size and type.

The iodine vapor technique used has been described before<sup>1-4</sup> and is briefly as follows:

1. *Preparation of Smears.*—A cotton applicator is inserted into the vagina and twirled lightly (one complete rotation) against the vaginal wall. The cotton end of the applicator is then rolled lengthwise over the surface of a clean glass slide. By rolling, rather than rubbing, a uniformly thin film of cells, with minimal clumping and cell distortion, results. The film dries almost immediately and may be stained at once.

2. *Staining of Smears.*—Staining is accomplished simply by laying the slide, face down, over a shallow dish containing Lugol's solution. Iodine vapors which arise insensibly from the solution suffice to stain the glycogen-containing cells in two or three minutes. Microscopic examination may be carried out immediately. Although stains made in this manner fade in twenty-four to forty-eight hours, restaining by the same method may be carried out repeatedly if subsequent examinations are desired.

Following is the system of grading, based on the glycogen and its intracellular distribution:

*Grade I.*—Complete glycopenia. Smears of this type contain only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris. In extreme degrees there is marked paucity of epithelial elements.

*Grade II.*—This grade is marked by a greater abundance of epithelial elements than Grade I. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm ("mottled cells"). Diffusely stained brown cells, usually of the small round variety ("deep cells") may also be present in small numbers. Many glycopenic yellow cells are also present.

*Grade III.*—A further increase in cell numbers is evident in this grade as compared to the preceding. The cells are larger and more regular. The diffusely stained cytoplasm has a light brown color. Noniodophilic yellow cells are also present in abundance.

*Grade IV.*—This grade is easily recognized by the presence, almost exclusively, of large, flat, deeply stained brown iodophilic cells, singly or in large clumps. This grade represents maximal estrogenic effect and corresponds to the smear of the normal proliferative or follicular phase.

The duplicate smears were stained by a slight modification of Geist and Salmon's technique,<sup>5</sup> the chief differences being that, (1) the smears were made from applicators as described for the iodine method, and (2) staining was done with ordinary carbolfuchsin. These changes are rather unimportant but did save a little time since the quickly prepared smears dried almost immediately, and the staining was practically instantaneous.

The Geist and Salmon technique, though requiring considerably more skill in microscopy than the iodine vapor stain, is, however, much simpler than the other rather impractically complicated older methods. It fails to demonstrate minor variations such as differences in cornification which are shown by some stains, but in general is quite adequate for satisfactory classification of the smears into four groups according to estrogenic deficiency or sufficiency, as follows:

*Reaction I.*—Marked estrogenic deficiency. Complete or nearly complete absence of large epithelial cells. Presence of variable numbers of small, deep or basal cells with large nuclei. Often abundant red and white blood cells.

*Reaction II*—Moderate estrogenic deficiency. Still a considerable number of deep cells but also a varying number of large epithelial cells. Fewer blood cells.

*Reaction III.*—Slight estrogenic deficiency. Predominance of large epithelial cells. Only occasional deep cells and blood cells.

*Reaction IV.*—Estrogenic sufficiency. Numerous large, clearly outlined, squamous cells with small nuclei. No basal cells or blood cells.

## Material

The vaginal smears for this study were obtained each day from 21 definitely postmenopausal women with varying degrees of estrogenic deficiency as indicated by both vaginal epithelial atrophy and cellular glycopenia. Three of these women received desiccated thyroid gland in one grain doses for 7 days, while the other eighteen were divided into six groups of three each to whom were given different estrogenic substances or combinations of such. The eighteen subjects who received estrogenic substances were the same as those whose iodine vapor smear findings were illustrated by Figs. 6 to 11 in the last report by Mack.<sup>4</sup>

TABLE I. DESICCATED THYROID GLAND—ONE GRAIN DAILY FOR SEVEN DAYS

PATIENT	STAIN	THYROID GLAND															
17	Iodine vapor	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Fuchsin	1	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2
19	Iodine vapor	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	Fuchsin	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2
20	Iodine vapor	2	1	1	1	1	1	2	2	1	1	1	1	1	1	1	1
	Fuchsin	1	1	1	1	1	1	1	1	1	2	1	2	1	1	1	1



Comparisons of the daily duplicate smears stained by the two methods are shown in the accompanying Tables. The digits correspond, of course, to the "grades" and "reactions" described above. Omissions indicate missing smears for the days indicated.

TABLE II. CRYSTALLINE ESTRONE—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRONE	
5	Iodine vapor	2 2 2 2 2 3 4 4 4 4	4 3 3 3 2 2 2 3 2 2
	Fuchsin	2 2 3 3 3 4 4 4 4	4 3 4 4 4 4 4
27	Iodine vapor	2 2 3 3 3 4 4 4 4 4	4 4 4 4 4 4 3 3 3 3
	Fuchsin	2 2 3 3 4 4 4 4 3	3 4 4 4 3 3 3
7	Iodine vapor	1 1 1 2 2 2 2 2 3 2	2 2 2 2 2 2 1 1 1 1
	Fuchsin	1 1 1 2 2 2 3 3 3	2 2 2 2 3 3 3

TABLE III. ESTRIOL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRIOL	
12	Iodine vapor	1 2 2 2 1 1 3 3 3 2	3 3 3 2 2 2 2 3 2 2
	Fuchsin	2 2 2 2 2 2 2 2 2	2 2 2 2 2 2 2
13	Iodine vapor	3 3 3 3 4 4 4 4 4 4	4 4 3 3 3 3 3 3 3 3
	Fuchsin	2 2 2 2 3 3 4 4 4	4 4 4 4 4 3 3 3 3
14	Iodine vapor	2 2 2 1 1 2 2 2 3 3	3 3 3 2 1 2 1 2 2 2
	Fuchsin	2 2 2 3 3 3 3 4 4	4 3 3 2 2 2 2 2

TABLE IV. ESTRONE, ESTRIOL MIXTURE—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ESTRONE, ESTRIOL	
2	Iodine vapor	2 2 2 2 2 2 3 3 3 4	4 3 3 2 3 2 2 2 2 2
	Fuchsin	2 2 2 2 2 2 2 2 3	3 3 3 3 3 3 3 3
3	Iodine vapor	3 2 2 2 3 2 3 3 4 4	4 4 4 2 3 2 3 2 2 2
	Fuchsin	2 2 2 3 3 4 4 4 4	4 4 3 2 3 4 3 4
4	Iodine vapor	2 2 2 2 2 2 4 4 4 4	4 4 4 4 4 4 3 2 2 3
	Fuchsin	2 2 2 2 2 3 3 4 4	4 4 4 3 4 3 3 3

TABLE V. ALPHA ESTRADIOL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	ALPHA ESTRADIOL	
23	Iodine vapor	2 2 2 2 2 2 3 3 3 4	4 3 2 2
	Fuchsin	1 1 2 2 2 2 3 4	
28	Iodine vapor	1 2 1 1 2 2 2 2 3 4	4 4 4 4
	Fuchsin	1 2 2 2 2 3 3 4	
30	Iodine vapor	1 1 1 2 2 3 3 3 3 3	3 3 4 4
	Fuchsin	2 3 3 3 3 3 3 3	

TABLE VI. DIETHYLSTILBESTROL—ORAL 1.0 MG. DAILY FOR TEN DAYS

PATIENT	STAIN	STILBESTROL	
8	Iodine vapor	2 2 3 3 3 3 3 3 4 4	3 3 3 3 2 2 2 2 4 2
	Fuchsin	3 3 3 3 3 4 4 4 4	4 4 4 4 3 3 2 2
10	Iodine vapor	2 3 3 4 2 3 3 3 4 4	4 3 3 4 3 3 4 4 2 3
	Fuchsin	2 3 3 3 3 4 4 4 4	4 3 3 3 3 3 2 2
11	Iodine vapor	2 2 2 2 3 3 4 3 4 3	2 3 3 2 2 2 2 2 2 2
	Fuchsin	2 2 3 3 3 4 4 4 4	3 3 3 3 3 2 3 2

TABLE VII. SODIUM ESTRONE SULFATE—ORAL 1.25 MG. DAILY FOR EIGHT DAYS

PATIENT	STAIN	SODIUM ESTRONE SULFATE	
21	Iodine vapor	2 2 2 2 3 1 3 2	4 3 2 3 3
	Fuchsin	2 2 2 3 3 3 4 4	
22	Iodine vapor	2 2 2 2 2 3 3 3	4 4 4 4 4
	Fuchsin	2 2 2 3 3 3 4 4	
24	Iodine vapor	1 1 1 2 2 2 2 2	3 2 2 2 2
	Fuchsin	1 1 1 2 3 3 3	

### Comment

Inspection of Table I shows no essential or significant vaginal epithelial changes associated with the administration of thyroid. Such was to be expected since there is little or no evidence that thyroid extract has any estrogenic effect, at least, for the short period of medication and observation in this test. These first three cases, then, may be regarded somewhat as controls. On the other hand, all the estrogenic substances caused marked changes both in the glycogen content and in the fuchsin stainable cytologic features. Variations in the cellular glycogen were interpreted in the article previously mentioned,<sup>4</sup> and therefore the discussion here need be largely concerned only with a comparison of the two staining methods.

As a check on the grading of the two methods, the earliest duplicate smears were compared. They came on the first or second days of medication and before there could have been any substantial effect from the treatment. These initial duplicate smears from the 21 women showed the identical grade or reaction in 14. In 5 instances, the iodine vapor smear was one grade higher, and in 2 it was lower.

Since Willson and Goforth<sup>6</sup> reported the reaction from diethylstilbestrol to be evidenced by an increase of the glycogen in advance of other cell alterations, it was thought that the same relationship might hold for the maximum reaction which would follow treatment with estrogenic substances. Actually, this tendency proved to be the case in only one-third of the 18 cases; whereas in 9, or one-half, the maximum change was evidenced first in the fuchsin preparations. In the remaining 3, the greatest reaction was noted by both methods on the same day. Regarding stilbestrol itself, it will be seen that our 3 postmenopausal women given this substance first showed the maximum reaction with the iodine vapor technique, by the fuchsin method, and in both smears at the same time in one instance each.

Of some importance, especially regarding the treatment of vaginitis, would be any difference for the two methods in the duration of the reaction obtained from the administration of estrogenic substances. For the 12 patients who had enough duplicate smears to permit estimation (Tables II, III, IV, and VI), there was no important difference in the number of days at the maximum reaction resulting from treatment, there being 67 days with the fuchsin smears and 63 with those stained for glycogen. It is also noteworthy that, in spite of variations in time of incidence as mentioned in the preceding paragraph, an equal degree of smear reaction was reached sooner or later with both methods in 9 of these 12 cases. In 2 of the remaining 3 women the fuchsin smears, and in the last instance those stained by iodine vapor failed at any time to attain the highest grade found by the other method.

In conclusion, then, it can be said that these comparisons indicate no constant or significant differences in grading or reaction for duplicate

vaginal smears stained by fuchsin or iodine vapor methods in untreated menopausal women, or after the administration of thyroid gland and various estrogenic substances. Therefore, in view of its rapidity and simplicity, the iodine vapor stain for glycogen appears to deserve previous recommendations.

Acknowledgment is made to Dr. Harold C. Mack for his kindness in permitting use of his material and for suggestions regarding the conduct of these comparisons.

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955 FISHER BUILDING

## EXPERIENCE WITH THE SIX HOUR RAT TEST FOR PREGNANCY\*

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**I**NNUMERABLE pregnancy tests have been described in medical literature. Most of them have one or more disadvantages which have kept them from being generally accepted. It was not until Aschheim and Zondek described their technique that there became available a pregnancy test which met most of the requirements for such a procedure.

A pregnancy test, in order to be of much value, must meet certain specifications: its degree of accuracy must approach 100 per cent; it must be reasonably rapid and relatively simple.

To meet these requirements, much experimental work has been done. It would seem that the ideal test should be a chemical one, thus removing the source of error inherent in all work which depends upon biological assay.

Last year, Salmon and Geist<sup>1</sup> and their associates at the Mount Sinai Hospital used, as a pregnancy test, an observation which had been made many times before. They reported that within six hours after the injection of the urine of pregnant women into suitable rats a definite erythema of the ovaries developed. This was constant and their results compared favorably with those obtained with the Aschheim-Zondek or Friedman tests. In our laboratory, in 107 cases, we have had the same experience.

### Technique

Female rats are used as the test animals. They must be about four weeks old and weigh about 30 grams. Since these animals have a spontaneous estrus cycle and ovulate spontaneously at maturity, they cannot be used when they become much larger. Two animals are employed and two cubic centimeters of urine are injected subcutaneously into each. After six hours, the animals are asphyxiated with illuminating gas. In positive cases, the ovarian hyperemia is manifested by a reddening of the ovary. This redness is grossly visible in good light. Usually the uterus, too, is edematous and red looking although the interpretation of the test depends on the ovarian and not the uterine conditions. In the negative cases, the ovaries are small and white and the uterus is a white, threadlike structure.

In 107 cases, the following results were obtained:

\*Presented at a meeting of the Brooklyn Gynecological Society, October 1, 1943.

## RESULTS IN PREGNANT WOMEN

	RAT TEST			FRIEDMAN TEST		
	TOTAL	POSITIVE	NEGATIVE	TOTAL	POSITIVE	NEGATIVE
1st trimester	39	37	2 (a, b)	20	18	2 (b, c)
2nd trimester	2	2				
3rd trimester	13	13				
Duration unknown	9	9				
Total	62	61	1	19	18	1
(eliminating dead fetus case)						

a—Test in rat negative but Friedman test positive. Clinically the patient was shown to be pregnant.

b—Both rat and Friedman test were negative. In this case the fetus had been dead for about 3 months.

c—Friedman test negative but rat test positive. This patient was shown to be pregnant clinically.

## RESULTS IN NONPREGNANT WOMEN AND IN MALES

	RAT TEST			FRIEDMAN TEST		
	TOTAL	POSITIVE	NEGATIVE	TOTAL	POSITIVE	NEGATIVE
Males	15	0	15	0	0	0
Nonpregnant Women	29	1 (d)	28	9	0	9
Totals	44	1	43	9	0	9

d—As this was one of the early cases, the error may have been due to inexperience in interpreting the findings.

## Comment

At the beginning of the study, samples of urine were tested from male students, known pregnancies and known nonpregnancy cases. The identity of the subject was not known to the individual reading the result. Later, rat tests were done on the urines submitted for routine Friedman tests and the readings were made before the Friedman tests were completed. In those cases where there was no Friedman test and the samples were received from an outside source, follow-up was requested on the basis of the clinical course. In this way it is felt that all possible sources of error have been covered.

After this careful investigation it was found that 61 women out of 62 who were definitely pregnant gave a positive rat test while in one the test was negative. In 19 of these pregnant women the Friedman test was also done with 18 positive and one negative result. It is interesting to note that in the instance in which the rat test was negative, the Friedman test was positive, and in the case in which the Friedman test was negative, the rat test was positive. One patient in whom the fetus had been dead for three months gave a negative rat test and Friedman test.

In 44 instances in which there was no pregnancy, 43 rat tests were negative and one was positive. In 9 of these in which the Friedman test was also done, no positives were obtained. It may be possible that the positive rat test which was obtained in a nonpregnant woman was due to inexperience in interpreting the findings since this was one of the early cases.

Certain technical and economic details may be mentioned. Since the rats are of value for a very short span of their life (about two weeks) it is necessary to have a large colony on hand so that young are always available. If possible, the results should be read in daylight since color determinations are notoriously difficult under artificial light. And it is well to be sure that the individual making the readings is not color blind. For this reason, women often do better than men.

In conclusion we feel that, although the number of cases reported is not large enough to warrant an absolute statement as to the value of this test, enough work was done and the results were sufficiently accurate to justify the assumption that this may prove to be a valuable addition to our laboratory tests for pregnancy. It certainly warrants further trial by ourselves and others. Although it does not obviate all the difficulties inherent in biologic testing, this method shortens the time from some 36 or 48 hours down to six hours.

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264 BERKELEY PLACE

## VOLVULUS OF CECUM AS A POST-PARTUM COMPLICATION

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LITTLE can be found in American medical literature associating volvulus of the cecum with pregnancy. The enlarging gravid uterus has been known to precipitate volvulus. An article appearing in the *British Medical Journal* for October 25, 1941, p. 577, presents the case history of a patient succumbing to volvulus of the cecum following a difficult high forceps delivery in a 38-year-old primigravida. The diagnosis was made at autopsy. The author called attention to the fact that surgeons are reluctant to resort to surgical intervention during the puerperium and that abdominal complications are accordingly neglected. He further stated that pelvic peritonitis, retroperitoneal hemorrhage, paralytic ileus, and abdominal catastrophes such as volvulus, all may produce abdominal distention and be found as post-partum complications.

A case of volvulus of the cecum, as an unusual post-partum complication, was currently observed in the family outpatient department of the U. S. Naval Hospital, Philadelphia. A primigravida, 33 years of age, presented herself in the dependent clinic on March 31, 1943. Her last menstrual period had occurred on October 25, 1942, the estimated date of confinement being August 2, 1943. Family history was non-contributory. The patient had typhoid fever at the age of 18 years. Gastrointestinal history revealed the presence of an obstinate constipation which had largely subsided after the second month of pregnancy. The prenatal course preceding her first visit to the dispensary had been normal.

The patient was a small, well-developed and well-nourished white woman of German extraction. Her usual weight had been 112 pounds. There was a weight gain of ten pounds the first five months of pregnancy. General physical examination was negative. The abdomen was enlarged to the size consistent with a five months' pregnancy and the uterus was in the midline. Pelvic measurements were considered to be adequate for a vaginal delivery.

The prenatal course was uneventful until the eighth month when the patient developed a mild pitting edema of the extremities. The laboratory examinations were consistently normal. The weight gain continued to 134 pounds, or a total weight gain of 22 pounds.

The patient was admitted to the family out-patient obstetrical floor at St. Agnes Hospital at 6:30 A.M. on July 21, 1943. Pains had begun three hours before and the head was deeply engaged in the left occiput posterior position. The head rotated spontaneously to an anterior position and a low forceps delivery was completed at 10 A.M. The placenta was expressed intact with an estimated blood loss of 300 c.c.

Reaction to delivery and anesthesia was normal and the patient was comfortable until 9:30 P.M. the day of delivery. At this time there was upper and lower abdominal distention which was relieved by rectal tube

\*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Navy Service at large.

and the removal of 500 c.c. of urine by catheter. The patient rested comfortably the remainder of the night. The morning of the first post-partum day the patient again complained of upper abdominal pain which was again relieved by rectal tube and the administration of one ampule of prostigmine. Temperature, pulse, and respiration were normal and the patient was still unable to void. By 11:00 P.M. of this day the patient again complained of severe upper abdominal pain. There was a soft, upper abdominal distention and the abdomen was not tender. Hot abdominal stupes were applied and a soda bicarbonate enema administered. This resulted in the passage of stool and flatus and relief of pain.

On the morning of the second post-partum day there was a moderate upper abdominal distention, but the patient was retaining fluids by mouth, expelling flatus, and temperature and pulse were normal. She was still unable to void. One ounce of castor oil was administered by mouth and four hours later there was a copious bowel movement with a reduction in the distention, and an almost complete relief of pain. One hour later, and for the first time since delivery, the patient vomited some undigested food. By 9:30 P.M. the distention had recurred and a consultation was requested from the surgical service of the U. S. Naval Hospital. Paralytic ileus and partial mechanical obstruction were considered to be tentative diagnoses. The patient was still afebrile; pulse rate of 80. Wangensteen suction was instituted and three units of plasma administered.

A flat plate of the abdomen taken on the morning of the third post-partum day was not entirely satisfactory because of gaseous distention, but it revealed a large bowel distention with no definite point of obstruction. Examination of the abdomen showed some visible peristalsis. Five hundred c.c. of citrated blood were administered. Following this the patient had a chill and temperature elevation to 103.5° F. Temperature returned to normal four hours later and the supposition was that the chill and fever represented a transfusion reaction. Distention remained moderate throughout the day.

On the morning of the fourth post-partum day, the distention was definitely accentuated, the abdomen was tender, no peristalsis could be discerned by auscultation and the patient's condition was obviously more critical. Temperature was mildly elevated and the pulse rate was increased.

At 2:00 P.M. on the fourth post-partum day, operation was done under continuous spinal anesthesia. The abdomen was entered through a small left rectus incision revealing a hyperemic peritoneum and an increase in intraperitoneal fluid. A huge sausage-shaped mass could be felt extending obliquely upward and to the left across the abdomen. As the incision was enlarged, a volvulus of the cecum and lower portion of the ascending colon spontaneously delivered itself. The mesocolon was edematous and definitely elongated and the bowel had rotated counterclockwise, allowing the cecum to occupy a position beneath the left lobe of the liver. The bowel was dusky, there were some breaks in the serosa, but no evidence of devitalization. Reduction of the volvulus was easily accomplished and cecostomy was performed, the cecostomy tube being carried out through a stab wound in the right lower quadrant. The abdomen was closed without drainage after the introduction of five grams of sulfathiazole crystals. Three units of plasma were given and the immediate postoperative condition was excellent.



Wangensteen drainage was continued. Intravenous sodium sulfathiazole was administered at eight-hour intervals, and plasma, citrated blood, and intravenous glucose solution were given. The patient was irrational on the first and second postoperative days. There was a mild jaundice which was thought to be hemolytic and associated with the transfusions. Maximum temperature elevation reached 103.4° F. The Wangenstein tube was removed on the third postoperative day, and the colostomy tube and all sutures were removed by the fourteenth postoperative day. The patient was discharged from the hospital on the twentieth postoperative, or the twenty-fourth post-partum day. Her bowel habits had been normal for one week at the time of her discharge.

This case constitutes an unusual complication following a normal delivery. We feel that delivery with the sudden emptying of the uterus was a contributory factor. A partial obstruction probably existed from the time shortly following delivery, becoming complete on the evening of the third post-partum day. It is conceivable that an exact diagnosis could have been arrived at preoperatively, and surgical intervention instituted at an earlier date.

## CURE BY PENICILLIN FOLLOWING REPEATEDLY UNSUCCESSFUL SULFONAMIDE THERAPY IN A PREGNANT WOMAN WITH GONORRHEA

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*(From the Kingston Avenue Hospital of the Department of Hospitals)*

PENICILLIN therapy has already been reported in a large series of cases by various investigators. In this country, Keefer and his associates have published a notable series covering a variety of infections. Their report included 129 gonorrheal cases treated by Mahoney and his associates in the United States Public Health Service, seventy-five of which have already been reported. To date Mahoney and Van Slyke have treated 179 cases.

It is, therefore, with humility that I present this single patient but I feel justified in doing so because the case has certain unusual aspects and was most carefully checked culturally and clinically during and after treatment. The report is also unique in that there was no alternative therapy possible. We know of no similar case noted in such detail.

F. C., female, white, single, nullipara, 21 years of age, was admitted to the Kingston Avenue Hospital April 16, 1943, pregnant six and one-half months, with a cervical culture positive for the gonococcus. The cervical smear was negative. Urethral smear and culture were negative, as was the blood Wassermann.

The findings after admission, however, disclosed a profuse purulent urethral discharge with smears and cultures positive for the gonococcus. Skene's ducts were thickened. The left Bartholin's gland was the size of a cherry, while the right was normal. Condylomata acuminata about a quarter of an inch in diameter were present on the labia majora. The vaginal walls were inflamed and trichomonads were found in the discharge. The cervix was bluish with small erosions on both lips. There was a profuse mucopurulent discharge which disclosed gonococci on both smear and culture. The uterus was soft and enlarged to two fingers-breadth above the umbilicus, and the fetal parts were easily outlined. Urine analysis, blood count and sedimentation rates were normal.

On the day following admission she was started on a course of sulfathiazole. This consisted of four grams of the drug given daily for seven days. Lactic acid douches were given for her trichomonas infection. On April 26, and 28, gonococci were found in smears and cultures of the urethral and cervical discharges. Clinically, the urethritis and cervicitis showed no improvement.

On May 5, she was started on a course of four grams of sulfadiazine and sixteen grams of sodium bicarbonate daily for four days. Gonococci persisted in both the urethra and cervix and the clinical picture was unchanged.

On May 13, she was given three grams of sulfapyridine daily for ten days. The urethritis and cervicitis persisted and gonococci were still found in cultures from each.

Having failed to effect a cure with sulfathiazole, sulfadiazine and sulfapyridine and fever therapy being contraindicated because of the pregnancy, it was decided to administer penicillin. We were fortunate

to secure 88,000 Oxford units.\* On June 9, administration of the drug by continuous intravenous drip was begun. Penicillin (8800 units) were dissolved in 1,000 c.c. of normal saline and repeated every six hours. The intravenous administration was continued over a period of sixty hours. The patient was kept on a soft diet and fluid intake and output were charted. Temperature, pulse and respiration remained normal. Cultures and smears were taken from the cervical and urethral discharges at 3- to 6-hour intervals during the penicillin treatment. In three hours, after 4,400 Oxford units of penicillin had been given, the first cultures were taken and found to be negative. Thereafter sixteen consecutive cultures and smears from both the urethra and cervix remained negative. Clinically, the patient improved and ten days after completion of penicillin therapy, she was sent home free of gonococcus infection. The cervical erosions were also almost completely healed.

On July 4, she was admitted to another hospital at term in active labor. Twenty-two hours later she was delivered spontaneously of a normal female infant weighing 5 pounds, 12 ounces. Puerperium was uneventful. Smears and cultures taken from the baby's eyes were negative for gonococci.

On August 11, 23, 25, and September 8, the patient returned for post-partum checkups. She showed the usual post-partum findings, with no evidence of gonorrhea. Cultures and smears from both urethra and cervix were negative at these times making a total of twenty consecutive cultures and smears.

### Comment

This patient was refractory to sulfathiazole, sulfadiazine and sulfapyridine. Fever therapy was considered to be contraindicated because of the risk involved. She responded dramatically to penicillin and remained culturally and clinically free of the disease despite the provocation of delivery. The child likewise showed no evidence of infection.

Although this is but a single case and one hesitates to draw conclusions, it is quite possible that further experience will disclose that smaller dosage is effective in gonorrhea. Extensive studies on the use of penicillin in sulfonamide refractory individuals has so far been limited to the male. It is well known that the more scientific study in gonorrhea resolves itself about the female who is the principal disseminating factor of the infection. Moreover, the presence of such naturally occurring provocative tests as menstruation and pregnancy enhance the value of female studies. It is hoped that the means will soon be available for such clinical evaluation.

Penicillin therapy was effective in producing a rapid laboratory and clinical cure of a sulfonamide-refractory pregnant individual, in whom fever therapy was contraindicated. The baby likewise was free from infection.

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\*The penicillin was furnished by Charles Pfizer & Company, Brooklyn, N. Y.

## VULVAR EDEMA COMPLICATING DELIVERY

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EDEMA of the vulva may occur at any time during pregnancy, but, except in labor, it is more of an annoyance than a complication. It is almost invariably associated with generalized anasarca, with cardiac or renal disease, with hepatic disease involving obstruction of the portal circulation, or with pathological conditions causing pressure on the venous return. The degree of involvement varies considerably. Occasionally, when of prolonged duration, gangrene has occurred.

The treatment is that of the underlying pathology. The patient should be given a complete physical examination, and then proper corrective measures should be instituted. Local treatment is mainly bed rest, preferably in the Trendelenburg position, to decrease the intra-abdominal pressure on the affected venous circulation. Hot applications to the perineum may be of some value.

Vulvar edema is rarely a serious complication of labor because the amount of swelling does not reach sufficient proportions to cause a soft part dystocia. If some obstruction is created, scarification or a deep episiotomy usually overcomes it. Asepsis must be strictly observed as secondary infection of the traumatized tissue is not uncommon.

The following case is reported to illustrate the extreme degree of this condition.

I. G., a 24-year-old, unmarried, white multipara, was admitted to the obstetric ward of Sinai Hospital for observation on March 27, 1943. She was a nonclinic patient, and had not received prenatal care. A previous pregnancy, 2 years ago, complicated by a severe pre-eclamptic type of toxemia, was terminated successfully by medical induction of labor and low forceps delivery of a living child.

For 10 days at home, the patient watched "swelling" develop in her lower extremities before consulting a doctor, who advised immediate hospitalization. On admission, the lower extremities were found to be very edematous, but the striking feature was the phenomenal size of the labia majora. The abdomen was so edematous that no accurate palpation of the fetus was possible. There was no history of headache, visual disturbances, nausea, or epigastric pain. Blood pressure was 150/180. Examination of the eye grounds showed a few tortuous vessels, slight overfilling of the veins, but there was no spasm of the arteries. General physical examination was negative except for the presence of aortic insufficiency. The lungs were clear. The liver and spleen were not palpable. The urine consistently showed 4-plus albumin (3 to 4 Gm. per 24-hour specimen). Output was poor; only 475 c.c. in 24 hours. Blood counts and chemistry were normal except for total proteins 5.1; serum albumin 2.6 per cent; serum globulin 2.5 per cent.

Fluids were limited to 1,000 c.c. daily. She was given 200 c.c. of 25 per cent glucose intravenously every four hours and one ounce of magnesium sulfate by mouth each morning. Two 500 c.c. plasma transfusions were administered in the hopes of raising the serum proteins. Despite this therapy, she excreted increasing amounts of albumin, the urinary output became dangerously low and her blood pres-

sure rose steadily until it reached a peak of 190/110 on the third day of hospitalization. The vulva had attained such proportions by this time that a severe degree of soft part dystocia was present. The labia were discolored, very tense, and it was impossible to part them (Fig. 1). Gangrene of the skin was feared, and the decision to interrupt pregnancy was inevitable. Cesarean section was decided upon as the procedure of choice after trial aspiration with a syringe had produced a negligible amount of fluid. Very extensive scarification of the skin would have been necessary in order to rupture the membranes, and then it would have been too doubtful that the obstruction could be overcome sufficiently to permit vaginal delivery.



Fig. 1.—The vulvar edema preoperatively. Note involvement of perineal body and rectum.

Under cyclopropane anesthesia, a low cervical cesarean section was performed. A living child was delivered and also an undiagnosed twin. Both children were in good condition. The patient withstood the operation very well, and had an almost afebrile postoperative course. The generalized edema was gone in three days, and the vulva showed marked improvement. At the time of discharge, the edema had completely disappeared. The patient and the babies were discharged on the sixteenth day in good condition. She had lost a total of 42 pounds during her stay in the hospital.

## MEIGS' SYNDROME

EDWARD KELEMEN, B.A., M.D., LONG BRANCH, N. J.

(From the Monmouth Memorial Hospital)

THE following case report illustrates clearly the need for a more widespread recognition of Meigs' syndrome. In this case the diagnosis was made preoperatively, but only after a dangerous delay, prolonged study and an accidental recognition of the condition.

Mrs. E. G., entered the medical service at the Monmouth Memorial Hospital on July 2, 1942. Her chief complaints were cough, dyspnea, weakness and diaphoresis. Her gastrointestinal, genitourinary and cardiovascular past history was negative. No history of tuberculosis could be elicited.

A physical examination revealed a well-developed, thin, forty-nine-year-old, white female lying on her right side. Temperature 100° F., pulse 108, and respiration 32. Respirations were rapid and shallow, the skin pale, cool and dry. Head and neck were negative. The right chest contained fluid up to the apex. The heart was shifted far to the left. The distended abdominal cavity contained fluid and an irregular, hard and movable mass measuring roughly 20 by 15 cm. and extending from the symphysis pubis to the umbilicus. Pelvic examination, carried out advantageously only after the removal of 5,500 c.c. of clear, serum-colored fluid, revealed an ovarian mass which was freely movable. A pigmented nevus was present on the mons veneris. The extremities were negative. Blood, Wassermann and Kahn tests were negative, the blood count normal. Blood urea nitrogen, blood sugar and serum protein were also at normal levels. Fluid from the right pleural and abdominal cavities was of a specific gravity of 1.012 and sterile. Chest roentgenograms revealed no evidence of pulmonary tuberculosis.

Surgical and medical opinion were agreed that this case represented a papillary adenocarcinoma of the ovary with pleural metastases, and therefore, advised against exploratory laparotomy.

A diagnosis of Meigs' syndrome was made by the writer following a delay of almost 12 weeks, during which time 43 liters were removed from the pleural and abdominal cavities, the fluid at all time being sterile and transudate in character.

On September 30, 1942, under sodium-pentothal anesthesia, Dr. Harold Kazmann removed an ovarian fibroma. The specimen was hard, irregular and nodular and measured 15 by 8 by 12 cm. Microscopic examination revealed that "the tumor is composed of fibroblasts, closely placed, forming a cellular structure. Nuclei are large and pale, but not anywhere do they show evidence of malignancy. Throughout the tumor are small masses of cells of another character, mostly poorly preserved, but here and there are seen epithelial cells uniform in structure with small, dark nuclei. Such masses have developed cystic spaces in many instances. The epithelial inclusions serve to identify this as a Brenner tumor, in many of which, the development of fibrous tissue is such as to almost entirely obliterate the elements. Such a tumor as this is, in consequence, essentially a benign fibroma. It is quite consistent with Meigs' syndrome.

*Pathological Diagnosis:* Brenner's Tumor.—The patient made an uneventful convalescence, was discharged and followed up as cured during the last eleven months.

This case is presented primarily because the underlying pathology was a Brenner's tumor.

## CHIARI'S SYNDROME

J. CRAIG POTTER, M.D., ROCHESTER, N. Y.

CHIARI in 1855 reported two cases of a syndrome which has occurred very rarely. It consists of amenorrhea with persistent lactation following delivery. In 1882 Frommel found one case in a study of 3,000 gynecological patients in Vienna. Sharpe<sup>1</sup> in 1935 reviewed the literature, finding in all, four papers on the subject.

As the condition is so rare and as none of the reported cases had a subsequent pregnancy, the following case seems worth recording.

Mrs. F. J., aged 32, was seen July 17, 1934. At the age of 23, an ovarian cyst was removed and an appendectomy done. In 1933, she was delivered by low forceps and episiotomy of a full-term baby girl weighing 8 pounds and 3 ounces. She did not menstruate following the delivery and her breasts continued to lactate. In 1934, desiring another child, she was sent to me by Dr. Mac Naughton Wilkinson for study and to determine, if possible, the cause of the amenorrhea and lactating breasts. The physical examination was negative except that the breast ducts were full of secretion and the uterus was atrophic. Routine laboratory tests, including a basal metabolism, were negative. Endometrial biopsy revealed an atrophic endometrium. The endocrine preparations of that day were tried without relief. They were thyroid, progynon in oil, and corpus luteum extract.

In 1941, the patient returned, stating that in 1940, her breasts had stopped secreting and her periods had returned. Her weight, 142 pounds was the same. The question was, could she become pregnant? However, on January 20, 1942, Mrs. F. J. came to the office having missed two periods. Examination showed a pregnant uterus but the breasts were not secreting.

On September 7, 1942, she was delivered of a 9-pound baby girl by the Bell modification of the Scanzoni maneuver. She was unable to nurse the baby because of insufficient milk. To date, November 2, 1943, she has not menstruated and her breasts are dry.

As far as I know, this is the only patient with Chiari's syndrome who has had a subsequent pregnancy and delivery. An x-ray of the sella turcica and sugar tolerance test would have been interesting, but there was nothing clinically to suggest difficulty in the pituitary gland.

### Reference

1. Sharpe, E. A.: Frommel's Disease, *AM. J. OBST. & GYNEC.* 30: 411-414, 1935.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Vaginal Infections

Perez, Manuel Luis, Arenas, Normando, and Blanchard, Oscar: Our Experience in the Treatment of Vaginal Trichomoniasis, *An. Inst. de Mat. y Asist. Soc.* 2: 63, 1940.

Manuel Luis Perez, Normando Arenas and Oscar Blanchard review the methods of treatment in general use for trichomonas vaginalis vaginitis. They found the infection in 32 per cent of nonpregnant women, and in 50 to 70 per cent of pregnant women. Of all the pentavalent arsenicals used the most successful was p-oxy-acetyl-amino-phenylarsenic acid with kaolin as a vehicle. The instillation of 2 Gm. of the drug is preceded by vaginal application of a solution of 1 per cent picric acid. Good results were obtained in 150 patients. There were no recurrences. The authors also used silver picrate, 0.5 Gm. to 3 Gm. of kaolin, to which they added suppositories of silver picrate during the first week. The treatments were repeated every five to seven days and most patients were cured after from four to six applications.

J. P. GREENHILL.

Brady, Leo, and Reid, Roger D.: The Treatment of Trichomonas Vaginalis Vaginitis With Lactobacillus, *Ann. Surg.* 115: 840, 1942.

The authors present a method in the treatment of a very common ailment. They do not feel that the discharge of trichomonas vaginitis is typical to any degree, but it can simulate any other type of vaginal discharge. Failures in diagnosis may be attributed to the fact that sometimes the condition is overlooked and, secondly, that a previous bimanual examination with some lubricant inactivates the protozoan. Another failure in diagnosis may be attributed to the preliminary douche before examination. It is the opinion of the authors that not only is acid therapy necessary, but that lactobacilli are also essential. A method was worked out whereby the authors inoculated sterile skimmed milk with lactobacillus bulgaricus and mixed it with sugar and milk sugar in such a manner as to form tablets. These tablets are then inserted into the vagina. The authors treated 50 cases in such a manner from 3 to 6 weeks and longer when necessary, with recurrences in only six cases. The relief is rather prompt. The importance of treatment for a few days each month around the menstrual time is stressed.

WILLIAM BERMAN.

### Menopause

Bennett, Henry G., Jr., and TeLinde, Richard W.: The Menopausal Syndrome, *J. A. M. A.* 118: 1341, 1942.

The authors describe their method of treatment of the menopause symptoms with the use of pure crystalline estrogen converted into pellets by compression of the substance in drilled machine ground steel plates. The number of implantations number from one to five and the average total weight of estrogen in each implantation was 40 milligrams. Ninety-three and four-tenths per cent considered the above treatment satisfactory. Improvement usually began within two weeks



following implantation and lasted an average of 16.2 weeks. There were no signs of toxic or systemic reaction. One case of abnormal uterine bleeding was encountered. The method compares favorably only with that of the injection of stilbestrol pellets subcutaneously, except that with the latter, the side reactions are more marked.

Another group of patients with theelin crystals in aqueous suspension administered hypodermically in total doses of 5 to 25 milligrams and satisfactory clinical results were obtained in only 59.3 per cent of twenty-seven patients. Oral natural estrogens given three times daily by mouth produced satisfactory results in only 46 per cent of the cases.

Patients in the acute phase of the menopause respond better than those with prolonged histories. Surgical castrates responded better to pellet implantation than either the irradiated or the physiologic group. In regards to the vaginal smear, it was found that symptomatic relief preceded any change in the vaginal smear. There was no evidence to indicate that the estrone pellets were responsible for bleeding in this group. No evidence of benign endometrial proliferation was noted when pellets of estrone were used, but this was noted when the diethylstilbestrol pellets were used. There is some evidence to indicate that estrone is the weakest growth stimulator of the various estrogens.

WILLIAM BERMAN.

Freed, S. C., Wisin, W. M., and Greenhill, J. P.: The Oral Effectiveness of Estrone Sulfate (Conjugated Estrogens-Equine) in Women, *J. Clin. Endocrinol.* 3: 89, 1943.

Estrone sulfate (premarin) is a naturally occurring estrogen in the urine of pregnant mares. According to laboratory evidence, it is several times more potent than free estrone by mouth when administered to spayed rats. Administered to 152 women in dosages of 1.25 mg., 0.81 mg., and 0.4 mg., three times daily, it was found through therapeutic standardization according to subjective response to be satisfactorily effective in relieving symptoms of the menopause. Optimal results were obtained with the higher dosage, while the lower dosage generally resulted in the relief of symptoms. The results obtained were generally superior to those obtained in comparison with 118 women who received daily 0.5 mg. and 1.0 mg. of diethylstilbestrol orally.

CLAUDE J. EHRENBURG.

Glass, S. V., and Rosenblub, Gordon: Therapy of the Menopause. Superiority of Conjugated Estrogens-Equine Over Diethylstilbestrol, *J. Clin. Endocrinol.* 3: 95, 1943.

Previous to the introduction of sodium estrone sulfate (premarin) climacteric patients were treated orally with estriol glucuronidate (cmmenin) and diethylstilbestrol. Introductory treatment in the severe cases with parenteral estrone or estradiol was frequent. In a preliminary study, eighty patients were administered sodium estrone sulfate with supplementary doses of diethylstilbestrol. The latter drug was soon found to be unnecessary for complete symptomatic relief.

The present report is based on the treatment of seventy-one menopausal patients with sodium estrone sulfate alone. Initial dosages of 2.5 mg. to 3.75 mg. daily which were gradually reduced to as low as 1.25 mg. three times weekly effected good results in 82 per cent of the cases, fair results in 10 per cent, and poor results in 8 per cent of the patients. Questionable complications were noted in two cases. Sodium estrone sulfate is safe, effective, and orally active therapy for the relief of climacteric symptoms.

CLAUDE J. EHRENBURG.

Sevringhaus, Elmer L., and St. John, Ruth: Oral Use of Conjugated Estrogens-Equine, *J. Clin. Endocrinol.* 3: 98, 1943.

An attempt to secure a more potent water-soluble and conjugated estrogen has led to the production of Premarin. Although for clinical usage, it is unnecessary to reduce the compound to a state of crystalline purity, standardization must be made with reference to purified estrone sulfate.

Genuine estrogenic potency of the material administered orally in dosages of 1.25 mg. to 5 mg. daily was demonstrated through the use of vaginal smears from eighteen menopausal women of whom nine were artificially induced by bilateral oophorectomy. Further evidence of this potency was indicated by the occurrence of uterine bleeding in two of the patients.

Symptomatic relief of climacteric symptoms was complete in twenty-two of twenty-five patients to whom the substance was given orally. Of the three patients without relief, other reasons seemed to account for the failure.

Comparison of the above results with use of the other estrogens in the same women was made in an attempt to determine the relative value per dollar cost to the patient. Although the comparisons did not result in definite equations, it could be stated that estrogens-equine were as effective per dollar as the other natural estrogens according to 1941 retail prices. Further, 1.25 mg. of estrogens-equine is at least as potent as 2,000 I.U. and may be better than 5,000 I.U. of estrogenic substances, and is as effective as 1 mg. of diethylstilbestrol.

CLAUDE J. EHRENBERG.

Gray, Laman A.: Clinical Study of a New Type of Estrogen Preparation for Oral Use, *J. Clin. Endocrinol.* 3: 92, 1943.

Premarin, a new type of natural estrogenic preparation, consists of the natural conjugated estrogens of pregnant mare's urine. The predominating estrogen is estrone sulfate and standardization is expressed in milligrams as such. The result of treating sixty-four menopausal women was gauged on the basis of symptomatic improvement and changes in the vaginal smear. Dosages were 1.25 mg., 0.62 mg., and 0.31 mg. daily by mouth. Symptomatic improvement and vaginal epithelial response was generally better with the highest dosage; 1.25 mg., administered daily for 7 days, and thereafter that amount every other day, gave as complete symptomatic relief for the usual menopausal symptoms as could be obtained with other types of estrogenic therapy, and produced a vaginal growth effect equivalent to that of diethylstilbestrol mg. for mg. Complications were relatively few, one patient experiencing nausea, and four patients experiencing uterine bleeding during the course of treatment.

CLAUDE J. EHRENBERG.

## Breasts

Speert, Harold: "Pale Epithelium" in the Mammary Gland and Its Experimental Production in the Rhesus Monkey, *Surg., Gynec. & Obst.* 74: 1098, 1942.

The author reviews the literature on "pale epithelium" in the mammary gland. In a study of 474 breasts obtained from 304 rhesus monkeys, five instances of atypical epithelium, resembling "pale epithelium" are reported. These all occurred in a special group treated with large amounts of estrogen, and 4 out of 5 were in castrates. The author is of the opinion that these pale cells represent metaplasia of normal mammary epithelium. These cells probably play no part in the development of carcinoma.

Bucher, N. L. R., and Geschichter, C. F.: *Pregnandiol and Estrogen Output in the Urine of Patients With Chronic Cystic Mastitis*, J. Clin. Endocrinol. 1: 58, 1941.

The term chronic cystic mastitis has been used for decades to denote a benign lesion of the breast which is neither inflammatory nor neoplastic. Recent studies indicate that the changes in this disease are associated with endocrine disturbance.

Chronic cystic mastitis or mammary dysplasia comprises three groups of cases. Mild or early cases with painful dense mammary tissue are usually referred to as painful breasts or mastodynia. Cases with more persistent and definite nodularity are referred to as adenosis, shotty breast or Schimmelbusch disease, after Schimmelbusch, who described microscopically the proliferative changes in this condition. The third group of cases known as cystic disease is usually unrelated to the other two groups. It is characterized by development of one or more cysts of appreciable size in women whose breasts were previously normal.

Nancy L. R. Bucher and Charles F. Geschichter (Johns Hopkins Univ.) report endocrine studies on a group of cases of chronic cystic mastitis. The group includes seven cases with mastodynia, five cases with adenosis, and four cases with cystic disease. The urine of the twenty-three patients was assayed for pregnandiol excretion, and for twelve of these patients estrogen excretion was also determined.

The endocrine disturbances in mastodynia and in adenosis are similar. Adenosis may be looked upon as a more advanced stage of mastodynia. This is borne out by the clinical histories. Nearly all patients with adenosis give a history of painful breasts. Although the majority of cases with mastodynia, when followed for a period of five to ten years, show spontaneous regression, a small group develop adenosis during such a period of time. In a series of 241 cases of mastodynia followed for more than five years, ten cases (5 per cent) developed adenosis.

From an endocrine standpoint, both mastodynia and adenosis show corpus luteum deficiency. Estrogen values may be normal. From another point of view, cases with mastodynia and adenosis may be looked upon as having a relative hyperestrogen secretion. Experimentally this viewpoint is justified, since in castrated rats estrogenic stimulation alone with pellet implantations or daily injections of five to ten of estrone for several months, produces the characteristic picture of mastodynia and adenosis.

It is not possible to state with assurance the endocrine disturbance in cystic disease. The opinion based upon the few assays performed and the experimental production of cystic disease in animals is that the cysts develop following prolonged or intense unopposed estrogen stimulation, or after the withdrawal of a previous estrogenic stimulation.

J. P. GREENHILL.

Shinkai, T., Ohgusa, M., and Miyasaki, Y.: *The Relation Between Supernumerary Breasts and Labor*, Jap. J. Obst. & Gynec. 24: 34, 1941.

The authors maintain that women with well-developed supernumerary breasts seem to be prolific and have multiple pregnancies. Sterility among such women occurs half as often as in women without supernumerary breasts.

J. P. GREENHILL.

Warren, S.: *Relationship Between Chronic Mastitis and Cancer of Female Breast*, Rev. méd. de Rosario 30: 829, 1940.

Warren studied 1,044 cases of chronic mastitis in which a portion of the involved breast was microscopically observed. The patients included women with chronic simple and cystic mastitis, Schimmelbusch's disease, Semb's cystic fibro-

adenomatosis, Cheatle and Cutler's hyperplasia, Aschoff's cystic mastopathy and Reclus' disease. They were observed for an average period of nine years after operation. Cancer did not exist in any patient at the time of operation. It developed in thirty-five some time afterward. Warren found that the incidence of breast cancer was six times as great in women who had had chronic simple or cystic mastitis as in those who did not. It was greater in women above 30 and before the menopause than in those at the menopause or after. A relationship exists between chronic mastitis and development of cancer, although either condition may develop in the absence of the other. Treatment of chronic simple or cystic mastitis consists of excision of the involved portion of the breast. The patients should be observed for a long period after operation. The appearance of nodules or cysts in the remaining portion of the breast is an indication for unilateral mastectomy. Bilateral mastectomy is not justified as a preventive measure.

J. P. GREENHILL.

### Pregnancy Complications

Hüssy, P.: *The Sudden and Unexpected Deaths in Pregnancy and Labor*, Schweiz. med. Wchnschr. 71: 1283, 1941.

Sudden death during pregnancy and labor may occur as the result of eclampsia, particularly eclampsia without convulsions. Likewise, sudden death may occur as a result of acute pulmonary edema and acute yellow atrophy. Other causes of sudden death which have been described in the literature are hyperemesis, pyelitis, toxic myelitis, rupture of the uterus without symptoms, placenta accreta, hemorrhage from placenta previa, cervical laceration and rupture of varicose veins. Occasionally sudden death may result from abortion, hydatid mole, badly performed Credé manipulation, and pulmonary embolism. Furthermore, exitus may be brought about suddenly by affliction of the brain, particularly apoplexy, brain tumor and brain abscess. Occasionally sudden death is due to diabetes and other disturbances of the endocrine glands.

A certain number of deaths have been due to diseases of the heart and aorta. Likewise, rupture of the abdominal viscus has been responsible for some sudden deaths. Sudden death from shock is not infrequent.

J. P. GREENHILL.

Hughes, Edward C.: *Hyperemesis Gravidarum*, New York State J. Med. 42: 1732, 1942.

The author describes pathologic changes encountered in cortical zone of three pairs of adrenal glands removed at autopsy in fatal cases of hyperemesis gravidarum. These changes went as far as hemorrhage and actual necrosis in places. Experimentally, similar conditions were produced in the adrenals of virgin rabbits following the injection of 60 c.c. of urine from patients suffering from hyperemesis. The thyroid also showed lower function in the experimental animals. Studies were carried out in normal pregnant women and those suffering from severe nausea and hyperemesis with the possibility of correlating the above findings with the metabolic changes encountered in normal pregnancy, and hyperemesis especially from the standpoint of fluid output and blood sodium levels. The author emphasizes the necessity of adequate intake of fluid, sodium chloride and glucose by mouth, or parenterally, if necessary. He recommends the administration of large amounts of vitamins B and C, and also the use of some form of adrenal cortical extract on account of the possible damage to the adrenals with consequent lowered adrenal function, and the resulting associated metabolic disturbances.

KARL M. WILSON.

Robillard, Gregory L., and Imprescia, Stelio Z.: Congenital Tuberculosis, N. Y. State J. Med. 42: 1955, 1942.

The authors present a case of a primiparous, tuberculous woman who was delivered of a premature infant at the seventh month which died twenty-five hours after birth. Autopsy revealed extensive tuberculous lesions in the lungs and also involvement of the spleen, liver, pancreas, adrenals, kidneys and portal and mesenteric lymph nodes. Tubercle bacilli were found in large numbers in the lesions. The placenta was grossly normal, but sections were not studied. This appears to be a true example of congenital tuberculosis. A discussion of the possible tracts by which the infection could gain access to the portal circulation is presented.

KARL M. WILSON.

Young, James: The Eclamptic Phenomenon and Placental Ischaemia, J. Obst. & Gynaec. 49: 221, 1942.

The author presents his own observations on placental blood changes, infarction, etc., in relationship to toxemias of pregnancy. In the toxemias associated with accidental hemorrhage both the free and the concealed type, Young feels that the bleeding antedates the toxemia. These individuals have usually some bleeding in the early months of pregnancy and are known to have an "abortion taint." This abortion taint when intrinsic in the constitution of toxemic women is antecedent to the toxemia. The fetus is not essential since the same process can occur in hydatid mole. The toxemia develops subsequent to the placental degeneration. It is related to the early stages of the process, and its severity is determined both by the extent of the placental involvement and by the interval during which the fetus survives in utero. Half of the placenta may be compromised before fetal death occurs. In some cases of concealed hemorrhage the toxemia may be grave.

The similarity of the renal lesion, and its clinical manifestations to the "crush syndrome" are also discussed.

WILLIAM BERMAN.

Young, James: Renal Failure After Utero-Placental Damage, Brit. M. J. 4276: 715, 1942.

Two obstetric conditions showing massive damage of placenta and uterine muscle are followed by renal insufficiency and azotemia. They are accidental hemorrhage and the trauma of labor.

The sequence of events is: (1) Tissue damage. (2) Shock in severe cases, sometimes fatal. (3) Anuria or oliguria, and rising blood urea with diuresis and recovery, or suppression and death. Five fatal cases are reported. They were subjected to clinical and pathologic study. The author has written the following summary: "The foregoing clinico-pathological study of the syndrome in concealed accidental haemorrhage suggests the following proximate causes: (1) The syndrome is determined by a massive utero-placental lesion of ischaemic origin. (2) The renal failure characterized by tubular degeneration and azotaemia is determined by a toxic derived from tissue autolysis. (3) The shock element and the haemolysis which are frequently present may have a similar origin."

FRED L. ADAMS.

Rabin, S., and Dulk, H.: Chorea Gravidarum. A Case Cured by Vitamin B<sub>6</sub>, Ann. brasil. de ginec. 14: 12, 1942.

The authors report a case of a 19-year-old girl in the second month of pregnancy who complained of vomiting. Fifteen days after her first visit, she complained of numbness, weakness and incessant movements of the left arm. Large doses of vitamin B<sub>6</sub> were given and the patient was relieved. Among the thirty-one members of the Brazil Society of Gynecology before whom this case was reported, eight mentioned that they had had sixteen cases of chorea gravidarum. This incidence of chorea may be due to the high frequency of avitaminosis in Brazil.

J. P. GREENHILL.

Corcoran, A. C.: Renal Aspects of the Late Toxemias of Pregnancy, West. J. Surg. 50: 622, 1942.

Hypertension in pregnancy represents a phase, latent or apparent, in the development of essential hypertension. Experimental renal hypertension with a rigid metal clamp (Goldblatt) parallels the pathologic and clinical findings observed in the human. The maintenance of cardiac output and peripheral blood flow as well as the arteriolar pathology are the same. Induced hypertension in dogs has been shown to be the result of the secretion of renin from the kidney with inadequate blood supply. The reaction of renin with a renin activator in the blood plasma produces an active pressor substance called angiotonin. The injection of angiotonin into dogs or the human will cause arteriolar constriction, increased cardiac effort and elevated blood pressure while peripheral blood flow to the limbs and skin is normal. The action of angiotonin mimics essential hypertension as seen in the human.

A study of changes in the blood flow through the kidneys can be rather accurately determined by diodrast clearance test. The rate of glomerular filtration can be determined by inulin excretion. Using these tests, it has been shown that most hypertensives show some reduction of renal blood flow associated with high filtration fraction. This proves that there is increased intraglomerular pressure which is the result of efferent arteriole constriction. The same phenomena can be reproduced by injection of angiotonin. It has been shown that there is an angiotonin inhibitor substance liberated from the kidneys. Extracts were, therefore, made of kidneys and injected into hypertensive animals and humans with significant but not consistent drops in blood pressure.

Eclampsyogenic toxemia is a disease peculiar to pregnancy in the human. It is characterized by decreased rather than increased extraction of water from blood in the glomerulus. Renal blood flow remains normal and since arteriole pressure is increased, one must assume that renal resistance, probably in the arterioles, has been greatly increased. This change is brought about by a swelling of the glomerular basement membranes. This disappears promptly after delivery. The pressor state in eclampsia is apparently of renal origin initiated by some dysfunction of the uterine contents. In contrast to the human, pregnancy in hypertensive dogs has a tendency to lower blood pressure to normal levels with recurrence of the hypertension promptly after delivery.

WILLIAM BICKERS.

Taylor, Howard C., Jr.: Relationship of the Hormones to the Toxemia of Pregnancy, J. A. M. A. 120: 595, 1942.

The consensus of findings among workers indicate that chorionic gonadotropic substances are elevated in the urine and serum of toxemic patients. The excretion of estrogens has been reported as being low in cases of severe toxemia.

Pregnandiol is low in the urine of toxemia patients according to some reports. As a result of these findings, patients have been treated with hormones both estrogenic and luteal. The findings indicate that neither estrogen or progesterone in any dose yet employed, has shown itself as a specific in the alleviation of the toxic signs of pre-eclampsia. These hormones may, however, exert some influence on a pre-existing toxemia of pregnancy. On the basis of studies made by the author, it appears that sodium and water retention of normal pregnancy is due largely to the steroid hormones manufactured by the placenta. It is doubtful whether the increased sodium retention of toxemia is simply an increase in this effect. The clinical signs of proteinuria, hypertension, and edema appearing in toxemia of pregnancy disappear rapidly during the first days or weeks of the puerperium which may again be conceivably due to the disappearance of the hormones of pregnancy. Other studies involving the anterior pituitary gland, the adrenals, and the thyroid need further study and elucidation.

WILLIAM BERMAN.

Winn, W. C., and Ware, H. Hudnall, Jr.: Hydatidiform Mole: A Report of Six Cases, Virginia M. Monthly 69: 678, 1942.

Hydatidiform mole occurs once in every 2,000 cases of pregnancy. Color, race and parity are of no importance. The six cases reported are from the obstetric service of the Medical College of Virginia Hospital, one of which was particularly interesting because it was the rare benign, penetrating type, which resulted in spontaneous rupture of the uterus. A review of these six cases leads the author to believe that the uterus is not necessarily enlarged out of proportion to the period of amenorrhea in cases of hydatidiform mole. Toxemia and the beriberi type of heart are frequently associated. The spinal fluid Aschheim-Zondek test is not always positive. Following the removal or expulsion of the mole, the patient should be followed with periodic Friedman tests to rule out the possibility of chorio-epithelioma.

WILLIAM BICKERS.

Tillman, A. J. B.: Classification and Medical Relationship of Hypertensive Albuminuric Pregnancy, J. A. M. A. 120: 587, 1942.

The author feels that an attempt at an ideal classification of hypertensive albuminuric pregnancy seems at present impossible. It is frequently difficult to establish the origin of the complication. This is especially true when patients present themselves during the last trimester of pregnancy with the findings of hypertension, albuminuria, and edema. Some of these patients had kidney disease before they became pregnant, but it is difficult to establish this fact late in pregnancy. Between the diseases acquired prior to pregnancy, and the convulsive states of pregnancy, there are many phases of hypertension-albuminuria and edema arising in pregnancy which demand clarification. The greatest number of cases consist of pure hypertension. This may arise at any time during pregnancy. One severe type is the sudden, acute severe hypertension which persists in the absence of albumin and edema. Some of these return to normal after delivery, but many of them continue to have hypertensive vascular disease throughout life. Many conditions of hypertensive albuminuric pregnancy cannot be clarified until after delivery. One must conclude that two or more syndromes may arise as a result of pregnancy and terminate in a convulsive state, or that the many syndromes which arise as a result of pregnancy are identical fundamentally.

WILLIAM BERMAN.

Dieckmann, William J., and Kramer, Sylvia: Proteinuria in Toxemia of Pregnancy, J. A. M. A. 120: 590, 1942.

Normally during pregnancy the same amount of protein appears in the urine as in a normal nonpregnant individual. The incidence of proteinuria in the authors' ante-partum clinic was 20 per cent. Proteinuria usually occurs during labor, especially if the latter is long, the contractions are of long duration and frequent. The cause is the muscular exercise. Infection in the urinary tract may also cause albuminuria. A daily excretion of more than 5 Gm. of protein in the urine for 10 days, or more, should suggest nephritis or nephrosis, as such a large excretion of protein, rarely, if ever, occurs in pre-eclampsia.

Patients with eclampsia excrete a large amount of globulin, and the ratio is 2 or 3 to 1. The protein is excreted through the glomerulus, and as the number of functioning glomeruli grow less, there is less protein excreted. The authors feel that true pre-eclampsia, or eclampsia, do not cause a permanent vascular or renal disorder.

The incidence of abruptio placenta was highest in the hypertensive and the nephritic group. The author treats his patients with high carbohydrate diets of approximately 2,000 calories. The maximum weight gain is adjusted to 7 to 8 kg. for the entire pregnancy. The protein intake should be 80 Gm. or more. Vitamin E has been helpful in preventing fetal death from placental infarction or abruptio placentae. One to three grains of thyroid are given to these patients daily. Salt intake is reduced to a minimum. Water balance is watched. Ammonium chloride in 1 Gm. gelatin capsules is given eight times daily for five days, and repeated after a five-day interval. Oliguria or anuria is treated by hypertonic glucose (20 and 30%) intravenously. The loss of protein should be balanced by diet, but cannot be prevented by increasing the protein intake.

Treatment of these patients depends upon the duration of the pregnancy, the severity of the symptoms and signs of the condition of the cervix. The patient who does not respond to treatment or has been neglected is treated by rupture of the membranes and/or the insertion of a bag if the cervical canal is less than 2 cm. long, or if there is no effacement by cesarean section under local anesthesia.

WILLIAM BERMAN.

Reekie, R. D.: Necrosis of the Anterior Pituitary Associated With Pregnancy and the Puerperium, West. J. Surg. 50: 293, 1942.

The syndrome of emaciation and death following necrosis of the anterior pituitary is reviewed by the author. It is stated that there was a total of 27 early post-partum necroses, and 21 with healed lesions who died of other causes reported up until 1938. Post-partum necroses occur most commonly after shock secondary to post-partum hemorrhage. Necrosis apparently does not occur following extensive hemorrhage in nonpregnant patients. Pregnancy so alters the blood supply to the anterior pituitary that thrombosis leading to ischemic necrosis may follow severe blood loss at delivery. A case is reported in which a primigravida, who had developed a moderate pre-eclampsia was seized by sudden, severe pain in the dorsolumbar area eight days before term. This was followed by vomiting, headache and convulsions. She was treated conservatively for eclampsia, and on the second day, developed hemorrhagic tendencies at the point of hypodermic needle punctures. Spontaneous labor ensued, and a macerated fetus was delivered approximately 24 hours after the onset of illness. She became anuric, and died in 68 hours after the onset. Autopsy revealed a large retroperitoneal hemorrhage extending from the pelvis up to the right kidney. There were numerous hemorrhagic areas in the skin and extensive necrosis of the anterior lobe of the hypophysis. There were very few histologic changes in the



liver and kidneys. The question is raised as to the cause of death. Is the anterior pituitary necrosis the result of the hemorrhagic diathesis, or may it be considered the etiologic factor in the production of this toxemic syndrome? The relationship of the anterior pituitary to liver function and water balance may be such that a disturbance of pituitary physiology results in widespread disturbances producing the syndrome described here.

WILLIAM BICKERS.

**Eastman, N. J., and Whitridge, John: The Prevention of Toxemia of Pregnancy, J. A. M. A. 120 729, 1942.**

The authors mention the declining incidence of maternal mortality due to eclampsia in the United States. These figures are good where good ante-partum care is available. Regular prenatal visits are of prime importance. The changes in blood pressure, weight and albuminuria are again stressed. The authors attach great importance to the education of mothers, in the form of printed matter, concerning the signs of pre-eclampsia and impending eclampsia. The usual dietary and sedative regime is again reviewed. The treatment of these cases depends entirely upon the parity and the duration of pregnancy. The more conservative the method, the better the end results. In eclampsia, the figures leave no doubt that radical treatment is deadly. Great stress is laid on the chronic hypertensive type of toxemia which according to the authors, is about 10 times more frequent now, than 5 years previously. These patients usually have hypertension to some degree before they become pregnant, and their pregnancy aggravates the condition. In this respect, they differ from the eclampsias. The treatment depends upon the severity of the process. The authors warn that in this group of patients, cesarean section should be reserved for severe cases in which conditions are such as to make rupture of the membranes unwise, usually the presence of a firm, long, closed cervix. It should be reserved for cases where difficulty with pelvic delivery is to be anticipated. The repeat toxemia patients, if allowed to go through successive pregnancies, eventually develop chronic vascular damage.

WILLIAM BERMAN.

**Urbanski, Adrian X., and Hutner, Cyril I.: Thrombopenic Purpura Complicating Pregnancy, J. A. M. A. 20: 754, 1942.**

The authors report a case of thrombopenic purpura which was followed for 11 years before operation, and 7 years after splenectomy. Before operation, she had many admissions for hemorrhages of one sort or another, and was delivered of a stillborn full-term fetus which manifested general petechial hemorrhages and localized hemorrhages in the skin and in the visceral cavities. Following splenectomy which showed the microscopic picture of thrombopenic purpura, she had three children in a period of six years with no unusual complications of hemorrhage. The first child had a few purpuric spots which disappeared in a few days, but the other two children were entirely normal.

WILLIAM BERMAN.

**Vilar, Rafael A.: Malaria in Pregnancy, Bol. Asoc. méd. de Puerto Rico 34: 222, 1942.**

Rafael A. Vilar states that many authors think that high fever and toxemia are the principal causes of fetal death in pregnant women who have malarial attacks. But Graham has found the intervillous spaces of the placenta filled with reticulo-endothelial cells instead of blood, and it is therefore possible that many abortions are the result of fetal death due to mechanical obstruction of the ma-

ternal blood in the placenta. The transmission of malaria to the fetus is still uncertain. In any case, malaria is decidedly dangerous for the fetus, and the pregnant woman who has acute or chronic malaria must be treated for her own sake, and for that of the fetus. According to the authorities on the subject, the ideal drug, especially in pregnant women, is quinine. The public and even some physicians are under the impression that quinine is dangerous in pregnancy and may cause abortion. However, most authors agree that in therapeutic doses, the drug does not produce contractions of the uterus and cannot induce premature labor; but if there are already slight uterine contractions, they may be increased by the use of quinine. Plasmochin and atabrin may be prescribed when quinine is contraindicated, but plasmochin is quite toxic and may cause the formation of methemoglobin; it should be given only under strict medical supervision and never alone. Atabrin is less toxic, but large doses may produce lesions of the liver and kidneys which are already under physiologic strain during pregnancy. Consequently, quinine is the drug of choice, and its only contraindication would be an idiosyncrasy of the patient.

J. P. GREENHILL.

Beruti, Joshue A., Diradourian, Jorge and Ahumada, Jorge Luis: Results in the Treatment of Eclampsia, *Arch. Clin. obst. y ginec. "Eliseo Cantón"* 1: 69, 1942.

Josue A. Beruti, Jorge Diradourian and Jorge Luis Ahumada have made a statistical study of the cases of eclampsia which were observed in the clinic from 1911 to 1937 inclusive. Among 49,904 pregnancies, there were 339 eclampsia, or 0.67 per cent: 46, or 13.5 per cent, occurred during pregnancy; 220, or 64.8 per cent, during labor, and 73, or 21.5 per cent, during the puerperium. The number of maternal deaths was 64, or 18.8 per cent. Comparison of the treatment used in each of the three stages shows that Strogauoff's method offers the greatest chance of survival for mother and child under all circumstances.

J. P. GREENHILL.

Rose, D. K.: Treatment of Pyelonephritis of Pregnancy, *West. J. Surg.* 50: 518, 1942.

Pyelonephritis of pregnancy may be either primary or a recurrence of an old infection. The exacerbation during pregnancy suggests the possibility of some interference with normal drainage in the urinary tract. In such cases a careful urologic search for ureteral stricture, stone, tumor, ureteral kinks, and displacements of the kidney must be made. Drug therapy is never effective in the presence of defective drainage. Lacerations at the time of delivery may damage the trigonal muscle; this results in postpartum urinary stagnation due to the failure of the internal sphincter to properly relax. Micturition is a voluntary-involuntary reflex. Voluntary contraction of the perineal muscles causes a descent of the trigon, which permits urine to escape into the posterior urethra which sets up a reflex stimulating the bladder to contract. This physiology of micturition demands that all anterior vaginal wall lacerations must be repaired from the urethral meatus back to the trigon. In the treatment of pyelitis with acute onset during pregnancy, the author recommends sulfathiazole and sulfadiazine, occasionally mandelic acid in *B. coli* infections. Postpartum urinary retention is classified under three types: (a) True postpartum, (b) Postoperative, (c) An association of the two. In the post-partum type the bladder fills with a sense of fullness in the lower abdomen, but no sensation of a desire to void; it is a pres-

sure anesthesia. In the postoperative type, there is pain on lowering the perineum and therefore, the patient refrains from doing so; and the subsequent involuntary bladder contraction is prevented. The author points out that urethral caruncle is an effect and not a cause, being always associated with urethrocele or cystocele. He favors intermittent catheterization of the uninfected post-partum bladder only for very short periods of time. If post-partum retention continues, an indwelling catheter should be left in place for several days. Emphasis is placed upon the treatment of the underlying pathology as well as the bacterial infection.

WILLIAM BICKERS.

**Veita, Henry R., Schwab, Robert S., and Brazier, Mary A. B.:** The Effect of Pregnancy on the Course of Myasthenia Gravis, *J. A. M. A.* 119: 236, 1942.

The authors review the subject thoroughly and present eight cases of their own. Patients may have both a relapse and a remission during the same pregnancy, the relapse often coming in the first trimester and the remission following. There is usually a complete remission of symptoms in the last two trimesters of pregnancy. When a remission takes place, all symptoms disappear. In general, the relapses during pregnancy are mild to moderate and usually do not cause undue anxiety when the patient is under complete control with prostigmine.

Before the use of prostigmine, abortion was frequently carried out usually at the end of the first trimester. In view of more recent experience with patients under prostigmine therapy, many, if not all, of these abortions would not now be indicated. Abortion, moreover, may not relieve the patient of her symptoms, or even prevent a fatal termination from the disease. In general, either with or without prostigmine, labor itself is not usually affected by the presence of myasthenia gravis. It is concluded that pregnancy, labor, or nursing does not affect the course of the disease unfavorably under present conditions of treatment.

WILLIAM BERMAN.

**Leon, Juan, Ferrari, Roberto A., and Gonzalez, Jose Maria Lascano:** Grave Intra-peritoneal Post-Partum Hemorrhage. Primary Tubal Pregnancy With Uterine Evolution, *Bol. soc. de obst. y ginec. de Buenos Aires* 20: 731, 1941.

The authors report the case of a primipara, aged 31, who some time previously had an induced abortion with resulting infection which lasted several weeks. Pregnancy and labor were normal, but expulsion of the placenta was delayed. Signs of intra-abdominal hemorrhage appeared but were ignored; Credé's maneuver was performed without result, and the placenta was extracted manually. Exploration of the uterine cavity then disclosed complete rupture on the right side. Subtotal hysterectomy was performed and the patient recovered.

At first thought, it would seem that the previous abortion was the cause of the accident; if the right horn were perforated during curettage and the patient survived, the uterine wall would be friable at this point. But this could not explain the lesions found in the specimen. It could not be an angular or an originally interstitial pregnancy. In favor of the latter were the dilatation of the interstitial portion of the tube and the presence of a corpus luteum on the involved side, but interstitial pregnancy generally causes rupture of the tube during the first months or, if rupture does not occur, the pregnancy continues to develop in the interstitial portion. There is consequently no other recourse but to take the previous curettage into consideration. Probably, the lesion caused by it had changed the anatomic structure and the resistance of the interstitial por-

tion of the right tube, and an interstitial or isthmo-interstitial nidation had occurred on the inflammatorily altered mucosa of the region. The ovum developed toward the uterine cavity where the pregnancy ended normally. During the initial stages of the evolution of the ovum and owing to its implantation, the tubouterine orifice was dilated and kept open by the development of the placenta. After birth, uterine retraction strangulated the tubal portion of the placenta and caused its retention. The rupture may have started during labor or during the contractions to expulse the placenta, and it may have been aggravated by the Credé maneuver; considering the thinning of the tube by stretching and by the action of the chorionic elements, it is surprising that the accident did not occur sooner. Hysterectomy was justified by the difficulty of repairing the large opening in the uterine angle, and by the fact that cuneiform resection could not guarantee satisfactory end results.

J. P. GREENHILL.

Romney, Harry: Treatment of Fracture of Femoral Neck in Pregnancy, *Rev. cubana de obst. y. ginec.* 4: 136, 1942.

A 29-year-old woman, in the eighth month of gestation, fractured the neck of the left femur. The fragments were nailed together. Parturition took place without untoward incident and the bone healed quickly. The author does not think pregnancy a contraindication to this method of treating fractures of the femur.

R. J. WEISSMAN.

Puglielli, Mario: The Serious Syndrome of Pernicious Anemia of Pregnancy, *Rassegna d'ostet. e ginec.* 49: 479, 1940.

The author presents a detailed case report of an obstetric case, treated in the eighth month of her pregnancy with four transfusions of whole blood, while suffering from a serious complication diagnosed as pernicious anemia of pregnancy. The author reviews several theories of the pathogenesis regarding this complication of pregnancy.

CLAIR E. FOLSOME.

### Puerperium

Collins, Conrad G., Jones, Jack R., and Nelson, Edward W.: Surgical Treatment of Pelvic Thrombophlebitis, *New Orleans M. and S. J.* 95: 324, 1943.

The high mortality associated with pelvic thrombophlebitis and the poor results obtained by conservative treatment, prompted the authors to adopt a radical surgical treatment. They have reported three cases treated by ligation of the ovarian veins and the inferior vena cava. In the first case, pelvic thrombophlebitis followed a low forceps delivery, fever and chills beginning on the seventh day. Using spinal anesthesia, the right ovarian vessels were ligated and the inferior vena cava ligated one inch proximal to the junction of the common iliaes. The second case followed a septic abortion. The third case followed a vaginal hysterectomy. In all cases, the temperature came to normal soon after ligation of the inferior vena cava. Although venous pressure in the lower extremities was elevated following operation, no edema developed. Postoperative sympathetic procaine block of the sympathetic chain is recommended to aid in the development of collateral circulation and relieve edema that might be found after operation.

WILLIAM BICKERS.

**Ricci, Guido:** Parametrium and Pelvic Cellular Tissue. Topographic, Physiopathologic and Symptomatology Study, Bol. soc. de obst. y ginec. de Buenos Aires 21: 402, 1942.

Discussing the physiopathology of the parametrium and the pelvic cellular tissue, Ricci points out the correlation between varicosities of the lower extremities and genitalia and parametrial lesions, the latter probably being the starting point for the former. Attention is called also to the syndrome of "pseudo-phlebitis" consequent to a parametrial process, which is to be differentiated from phlegmasia alba dolens by the absence of the venous cord and of pain in the femoral region.

In examining the parametrium, the author prefers monomanual to bimanual palpation, claiming that the finger in the vagina is the one which receives the best orientation with the least traumatization. Bimanual palpation should be complementary only, to finally establish the topographic relations of the parametrium with the structures above it. The examination of the anterior parametrium is completed by introducing a rigid metallic sound into the urethra thus facilitating vaginal digital examination. Rectal palpation and a combined recto-vaginal examination is recommended for examination of the posterior parametrium. Regarding the examination in acute parametritic processes, Ricci maintains that when examination is done with one finger with utmost care and gentleness, the danger is purely speculative, while the information obtained is of paramount value. Clinical examination of the parametrial tissues should be supplemented by radiography of the colon, hystero-graphy, cystoscopy, rectoscopy and, if necessary, by exploratory puncture.

J. P. GREENHILL.

**Leopoldo, Perez Rojas:** Prophylaxis and Treatment of Puerperal Infection, Rev. cubana de obst. y ginec. 4: 199, 1942.

Leopoldo Perez Rojas states that 21,101 patients were delivered at the Municipal Maternity "America Arias" of Havana from 1937 to 1941. There were one hundred cases of puerperal infection, with eight deaths, or 8 per cent of the infected cases and 0.037 per cent of the total number of deliveries. Five of the patients who died were already infected on admission; the other three had had symphysiotomies.

Puerperal infection was greatly decreased under the influence of simple general prophylactic measures. Preventive treatment, without waiting for the appearance of signs of infection in any woman with more or less complicated labor ending with a difficult intervention, will decrease obstetric morbidity; prophylactic chemotherapy is used at the Municipal Maternity. There are no aseptic labors in the bacteriologic sense of the term, because many pregnant women carry in their genital tract organisms living as saprophytes which, during labor and the puerperium, become virulent as the defenses of the body decrease; another cause is genital metastasis from a remote focal infection (tonsillitis, grippe, etc.) or spreading of a neighboring infection by the lymphatic route. Therefore, sulfamide chemotherapy is used to combat the endogenous infections which may arise. In labors over 24 hours' duration, premature rupture of the membranes, vaginal examination, etc., sulfamides are given before delivery in doses of 5 to 6 Gm. a day, to maintain a concentration of 6 to 8 mg. per 100 c.c. in the blood. Oxytocics are also given during the post partum. The small amounts of the drugs eliminated in the milk do not contraindicate nursing.

J. P. GREENHILL.

## Correspondence

### The Reaction of the Human Uterus to Epinephrine

To the Editor:

I have read with interest the letter of Dr. Rucker in the August, 1943 issue of the *American Journal of Obstetrics and Gynecology* (page 330) regarding our report on the reaction of the human uterus to epinephrine. I particularly appreciate his constructive criticism, for he speaks from the wide experience of 91 cases of contraction rings; my own obstetric experience in the supervision of 7,000 deliveries has afforded me the opportunity to see only one and perhaps one other mild case of contraction ring dystocia. The combined experience of the diplomates of the American Board of Obstetrics and Gynecology on the staff of the University of Nebraska is 8 cases in 27,000 deliveries. Apparently the incidence of this condition varies widely. Either there has been an epidemic of contraction rings in Dr. Rucker's community, or his obstetric experience has included an astronomical number of deliveries.

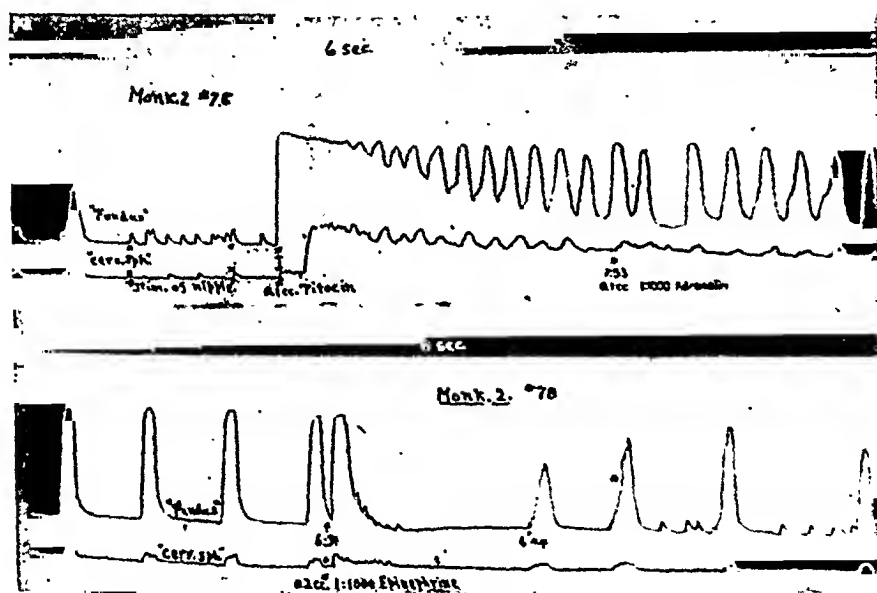


Fig. 1.—Photostatic copy of a chart of monkey uterus published by Ivy, et al.: in *AM. J. OBST. & GYNEC.* 22: 396, 1931.

This chart is an intrauterine tracing of a monkey showing both fundal and cervical contractions.

In both sections of the tracing the uterus reacts by premature contractions, followed by compensatory pause. This pause is approximately equal to the dropped beat. Also note that the cervix follows the fundus.

I am sorry that Dr. Rucker does not approve of India ink tracings for publication; however, if he will refer to his own published "originals" in the *Southern Medical Journal* 18: 912, 1925, it is noted that they have been reproduced so poorly that no other investigator can study them critically. Also, it will be noted that these patients received a number of drugs (adrenalin, novocain, hyoscine, chloral hydrate, paraldehyde, pituitrin, and quinine) so that it becomes impossible to interpret how much of the observed response was due to the adrenalin *alone*. Our experience in experimental work has convinced us of the impossibility of interpreting observations made during the administration of a multiplicity of drugs.

Apparently from Dr. Rucker's letter he failed to look up published graphs of Ivy, Woodbury, or Bourne. We had requested that these graphs\* be republished with our paper for comparison but this seemed undesirable. If these graphs are compared with those of our study, it is seen that they are very similar if not identical. In each case there is an extra contraction of the uterus followed by a pause. We interpret these graphs to indicate that the uterus responds to ad-



Fig. 2.—A composite graph of pressures in which the lower tracing represents the net intrauterine pressures. Photostatic copy taken from work published by Woodbury, et al.: *Am. J. Physiol.* 121: 648, 1938.

While this study was done on intact human uteri, it was not designed to demonstrate uterine contractions per se, but rather uterine tone. In the bottom curve of this graph one notes the effect of the injection of adrenalin. There is a rise in uterine tone followed by 2 uterine contractions and the fall in uterine tone. In the text Dr. Woodbury states:

"The effect of intravenous administration of 0.1 mg. epinephrine hydrochloride (see Fig. 13) is to produce a marked rise in blood pressure and intra-uterine pressure. The uterine contraction is stronger and much more abrupt in onset than the normal contractions. . . . The relaxation is slower is anything than normal and followed by two quickly succeeding smaller contractions. After this response uterine excitability seems somewhat lessened to return soon to normal."

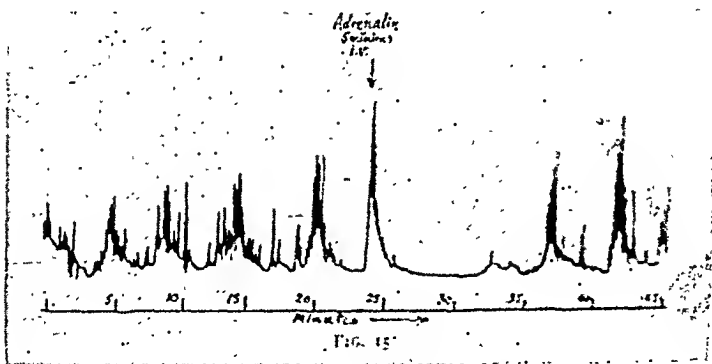


Fig. 3.—Photostatic copy of a graph published by BOURNE, et al., on human uterine strips published in the *J. Obst. and Gynaec. Brit. Emp.* 34: 272, 1928. In the text these authors state:

"Nevertheless, the view that adrenalin exercises an inhibitory effect on the pains of labour, required for its support less equivocal evidence than this, and in another patient, in whom we recorded a rapid succession of six pains during 25 minutes, an injection of five minims of adrenalin was made into the median vein. This injection (see Fig. 15) was followed by a complete cessation of uterus contractions during 12 minutes, after which the pains began again."

I accept the graphs of Dr. Bourne; but I am inclined to differ with him on the interpretation. If you will take a ruler and draw the peak lines of uterine contraction you see at once that the contraction stimulated by adrenalin is displaced in rhythm and augmented in intensity. The so-called 12-minute refractory period represents approximately 2 uterine contractions, so that we have in effect only one dropped beat.

It is my impression that this inhibition is a refractory state in the muscle due to muscular activity rather than to the adrenalin itself, for in each circumstance this period of inhibition is approximately the same length (2 uterine contractions). This inhibitory state is always preceded by an extra contraction.

\*These graphs are reproduced here for comparison.

renalin by contractions, and that the apparent inhibition is a compensatory pause resulting from muscular activity.

After these graphs have been studied by Dr. Rueker we would appreciate having his interpretation of the curves.

As I read the letter it appears that our differences of opinion are primarily a question of clinical interpretation. To this we are entitled. I would be very much interested in Dr. Rueker's experience with adrenalin *alone without any other form of treatment or interference* (anesthesia, sedation, parenteral fluids, forceps, version and extraction, bag). His wide experience of 91 cases of contraction ring dystocia has afforded him a privilege which few others have had to study the action of adrenalin alone. May I inquire how often he has used adrenalin *alone* and with what results?

WILLIS E. BROWN, M.D.

OMAHA, NEB.

SEPTEMBER 16, 1943.

### Reply From Dr. Rueker

To the Editor:

Your favor of September 27, requesting a reply to Dr. Brown's letter came in due time. I am sorry that I have taken so long to answer it.

In regard to the first of the two questions, interpreting Dr. Brown's graphs and those of Ivy, Bourne, and Woodbury, I would say that without seeing the patient at the time the graphs were made, their interpretation would be as difficult as giving an opinion on a microscopical section of tissue without knowing something of the history of the patient. In the *Journal of Laboratory and Clinical Medicine* (10: 390, 1925), I discussed some of the difficulties of interpreting hysterograms and showed that extraneous and extrauterine phenomena cause tremendous differences in uterine pressure, as shown on the hysterogram: I also showed that a psychic influence frequently had marked effect. Fig. 13 of the article shows a hysterogram in which there is a cessation of uterine contractions following an attempt at giving caudal anesthesia. I was unable to locate the sacral hiatus and gave the patient no drug whatever, nevertheless, the contractions ceased for 28 minutes. Furthermore, this article inadvertently shows another complication that might occur as there is a mixup of the figures and legends. The printer changed them about so that Fig. 11 which reads "Internal hysterogram showing cessation of uterine contraction for an hour and 15 minutes after sacral anesthesia with novocain and adrenalin," with no cessation. Fig. 12 shows the cessation of contractions for one hour and 15 minutes. Because of these difficulties, I would hesitate to offer an interpretation of graphs by such authorities. However, I do feel that one-half minim of adrenalin is an inadequate dose upon which to base an opinion that adrenalin does not cause a pregnant uterus to relax.

As to the second question, i.e., the number of times I have used adrenalin alone and the response of the uterus to adrenalin, it would be quite difficult to answer this question categorically as this work was done nearly twenty years ago, and no cross-reference was kept of the records so that it would be practically impossible to get out all the cases that were studied. In my article in the *Southern Medical Journal* (17: 412, 1925), I reported the first cases that I studied in reference to the effect of adrenalin. Case 3 had no previous medication. Case 5 had only a proctoclysis of 5 per cent glucose solution previous to the administration of adrenalin which was followed by cessation of contractions for 30 minutes. Case 7 had no previous medication and had no effect from adrenalin. Case 8 had no previous medication and had a definite diminution of contractions after 2 minims of adrenalin, hypodermically. Case 9 had no previous medication and had a definite diminution of the strength of contractions after adrenalin. Case 10,



that of an abortion on account of pyelitis, had no previous medication and no appreciable effect from adrenalin. Case 11 had glucose per rectum previously, and after adrenalin the contractions ceased for 26 minutes. Case 12 had no previous medication and after adrenalin there was a diminution in the strength of contractions. Case 16 had no previous medication. After adrenalin the contractions were of less force for ten minutes.

I think this also covers the supplementary question as to the length of time that the uterus remains quiescent after administration of adrenalin.

M. P. RUCKER, M.D.

RICHMOND, VA.

OCTOBER 22, 1943.

### Final Note From Dr. Brown

*To the Editor:*

There are two points of interest in Dr. Rucker's letter of October 22, 1943.

The first relates to the psychic and other factors which he suggests influence uterine contractions. It would be a most unusual coincidence if the same set of extraneous circumstances prevailed in Mr. Bourne's labor room in England in 1927, in an anesthetized monkey in Dr. Ivy's laboratory in Chicago in 1931, in Dr. Woodbury's studies of laboring patients in Atlanta, Georgia, in 1937, and in post-partum patients in Omaha in 1941. The dosage of epinephrine has varied widely with each of these investigations (from  $\frac{1}{2}$  to 6 minims).

Nevertheless, the curves of each of the four investigators are the same.

The second point is covered in Dr. Rucker's last paragraph and becomes self-explanatory when reduced to chart form.

EFFECT OF ADRENALIN ON UTERINE CONTRACTIONS  
(WITHOUT OTHER MEDICATION)

CASE NO.	INHIBITION	DOUBTFUL	NO EFFECT
%	3-5-11 36%	8-9-16 36%	7-10 28%

Thus when epinephrine is used alone it exhibits very doubtful inhibitory effect.

WILLIS E. BROWN, M.D.

OMAHA, NEB.

NOVEMBER 3, 1943.

# Society Transactions

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## THE NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCT. 12, 1943

The following papers were presented:

An Unusual Intra-abdominal Surgical Complication in the Puerperium. Edwin G. Langrock, M.D.

Surgical Complications During Pregnancy. Charles G. Child, III, M.D. (by invitation) and R. Gordon Douglas, M.D. (For original article, see page 213.)

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## THE OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JUNE 5, 1943

A special meeting to commemorate the Seventy-Fifth Anniversary of the Founding of the Society.

The Program consisted of the following papers:

The History of the Society. Lewis C. Scheffey, M.D.

Personal Reminiscences. Daniel Longaker, M.D.

The Present Status of the Society. John C. Hirst, M.D.

The Future of the Society. Edward A. Schumann, M.D.

# Necrology

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**S**AMUEL HERBERT GEIST, A.B., M.D., gynecologist, died in New York City, December 14, 1943, at the age of 58. He was a graduate of the College of Physicians and Surgeons, Class of 1908, interned at Mt. Sinai Hospital in New York, with which he was continuously associated, until the time of his death, since 1937 as Attending Gynecologist. He served as Captain in the Army Medical Corps with the American Expeditionary Forces in France, 1917-1918. Well known for his research work in the field of hormones and ovarian tumors, he was the author of an extended textbook on the latter which was published recently.

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## Item

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### American Board of Obstetrics and Gynecology, Inc.

#### Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944, at 2:00 P.M.

Arrangements will be made so far as is possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 12, 1944, Part I examination, who are entering Military Service, or who are now in Service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding them to the office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

Headquarters for the Part II examination will be the Hotel William Penn, Pittsburgh, Pennsylvania, from June 7 to 13, 1944. Notice of the exact time of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations as they apply to civilian candidates.

Applications for the 1944 examinations are now closed.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

DECEMBER 18, 1943.

PAUL TITUS, M.D.

# American Journal of Obstetrics and Gynecology

VOL. 47

MARCH, 1944

No. 3

## Original Communications

### AN EXPERIENCE WITH ONE HUNDRED CASES OF CONTINUOUS CAUDAL ANALGESIA

C. O. McCORMICK, M.D., CARL P. HUBER, M.D., JOHN F. SPAHR, M.D.,  
AND CHARLES F. GILLESPIE, M.D., INDIANAPOLIS, IND.

*(From the Department of Obstetrics, Indiana University School of Medicine)*

AS OBSTETRICAL anesthesiology progresses old methods will be discarded or modified and continued, and newer methods will be evaluated and accordingly accepted or rejected.

The most recent method, continuous caudal analgesia, announced in October, 1942, by Hingson and Edwards,<sup>1</sup> has received unusual medical and lay publicity, and has been popularly investigated by leading American clinics.

The results of several of these studies have been published, and in the majority of instances, especially those covering the larger series of cases, there has been much favorability, in some instances to the degree of enthusiasm.<sup>2</sup> However, a few investigators<sup>3-6</sup> have been impressed by certain potential major hazards the method carries, and warn against its routine and indiscriminate use.

It is the purpose of this presentation to give the results of our experience with the procedure and to correlate them with those of others, thereby contributing to the method's ultimate evaluation as an implement in the armamentarium of obstetrical anesthesia.

Our study covers one hundred cases conducted in the obstetrical department of Indiana University. Fifty-one of the deliveries were performed at the William H. Coleman Hospital for Women and forty-nine at the Indianapolis City Hospital. The technical conduct of the anesthesia was done entirely by the two co-authors, Dr. John F. Spahr,

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

obstetrical resident at the Coleman Hospital, and Dr. Charles F. Gillespie, obstetrical resident at the Indianapolis City Hospital.

Our interest in this form of relief has been from the outset more than casual, it having been stimulated by the original work done in our department by a former resident, Dr. Samuel Manalan, who inaugurated the ureteral catheter instillation method in caudal block anesthesia. He applied the method only during the perineal stage. His technique and the results of his study, based upon forty-six cases, were reported in the October, 1942, issue of the *Indiana State Medical Journal*.

Except for the ureteral catheter instillation used in twenty cases, the special malleable needle technique described by Hingson and Edwards<sup>7</sup> was employed throughout our series. The anesthetic agent used was a 1.5 per cent solution of metycaine.\* The largest amount of the solution used in any one case was 1,030 c.c., representing a total of fifteen grams of metycaine. This amount was administered over a period of thirty-eight hours with no ill effect resulting to either the mother or infant except for a localized abscess at the hiatus which cleared up in ten days after incision and packing.

Forty cases, or forty per cent of our series, including two cesarean sections, were completely relieved of pain. Another forty cases (40 per cent) were partially relieved. Eighteen of this group although not completely relieved were sufficiently so as not to require additional relief, while the remaining twenty-two required supplementary anesthesia. Included among these twenty-two cases given supplementary relief were five cases of slipping needle, three cesarean section cases, and one subarachnoid injection case.

The subarachnoid case manifested anesthesia up to the second thoracic, muscular paralysis of the abdominal wall and the lower extremities, a temporary suspension of uterine contractions, and a fall in blood pressure from 120/85 to 80/60. However, the patient did not go into shock. This reaction followed the following procedure: Twenty minutes after the initial 8 c.c. of metycaine had been injected and there had resulted no anesthesia, the needle was withdrawn and reinserted. Upon aspirating for spinal fluid, a fluid slightly tinged with blood was obtained. Through misjudgment this was thought to be anesthetic fluid and not spinal fluid. Ten minutes after injecting a second 8 c.c. an additional 22 c.c. was injected. Undoubtedly the dura had been penetrated at the second insertion of the needle.

Twenty cases, or twenty per cent, of the entire series were complete failures. Eighteen of these twenty cases were due to inability to enter the hiatus properly. The remaining two were due to intravenous injection, necessitating the discontinuance of the method.

Undoubtedly the low per cent of successful and the high per cent of partial relief cases and complete failures can be attributed in a large measure to the inexperience of the two authors who conducted the in-

\*Eli Lilly & Co. furnished the metycaine used in this study.

stillations. General experience has shown that results improve perceptibly as familiarity with the technique increases. Our results would have been more favorable had the series been conducted by one instead of two anesthetists. On the other hand, it must be observed that, although novices, they were sufficiently skillful and careful to avoid breaking any needles or catheters, and such accidents as penetrating the rectum through the sacrococcygeal ligament.

Our maternal complications, although not of a large variety, did in a few instances manifest seriousness. Two outstanding cases were those of respiratory and vascular collapse. Both were cesarean section cases, and will be presented in detail presently under "fetal complications."

Our most frequent complication was drop in blood pressure. A majority of the cases experienced this reaction to some degree, twelve (15 per cent) of the eighty analgized cases had a fall of over twenty points in the systolic level. Siever and Mousel<sup>8</sup> report having minimized the fall in blood pressure and the elimination of cardiovascular collapse by including epinephrine in the anesthetic solution.

We had one case of localized infection at the site of injection. This occurred in the thirty-eight-hour instillation case referred to earlier in the paper. Another protracted case developed neurologic symptoms. This patient had a forty-eight-hour labor, during the last twenty-four hours of which she was given continuous caudal analgesia. During the last twelve hours of her analgesia and the twenty-four hours following she presented a positive Kernig's sign, a stiff neck, and a positive Brudzinski. These symptoms gradually diminished and disappeared during the twenty-four hours following the anesthesia. Lumbar puncture was not considered necessary. There were no subsequent ill effects.

The welfare of the fetus was involved in but two instances, but unfortunately to a catastrophic degree. One infant was lost and the other was permanently damaged. In that a survey of the literature does not reveal similar accidents, summarized reports of these two cases are herewith given.

CASE 1 (66720).—Age 28. Gravida viii, para v, abortions 2. This patient had been delivered by cesarean in 1936 because of eclampsia developing during her fourth pregnancy. Cesarean was repeated in 1938 and she subsequently had two spontaneous abortions. Her present pregnancy had been normal with a maximum blood pressure of 134/92 and without albuminuria or edema.

Elective cesarean at term was planned for March 5, 1943. She received seconal grains 3 at 9:00 P.M. the day before operation and nembutal grains  $4\frac{1}{2}$  at 7:00 A.M. on the following morning. At 8:11 A.M. 8 c.c. of  $1\frac{1}{2}$  per cent metycaine solution was injected following entrance into the caudal canal without difficulty. Ten minutes later 22 c.c. of  $1\frac{1}{2}$  per cent metycaine solution was injected and atropine sulfate grain  $\frac{1}{150}$  was administered hypodermically. This was followed in twenty minutes by an additional 15 c.c. of anesthetic solution. The level of skin anesthesia reached the costal margin on the

right side and was slightly lower on the left. Twelve minutes following the last injection and forty-five minutes following the initial injection the patient's color became very pale with some cyanosis, the pulse increased to 130, and the blood pressure was 60/40. She became nauseated and vomited. At this time the fetal heart rate dropped to 60 per minute. Fetal movements were active and for a period of time became unusually violent. Oxygen was immediately administered and 40 c.c. of 50 per cent glucose solution in distilled water were given intravenously. She received ephedrine sulfate grain  $\frac{3}{4}$  hypodermically. Fifteen minutes later the blood pressure was still 60/40 and the fetal heart rate was 70 per minute. During the next hour her condition gradually improved, the blood pressure returning to 130/80 and the fetal heart rose to 100. She received during this time 700 c.c. of 10 per cent glucose solution intravenously and oxygen continuously. The operation was postponed and was performed without incident twenty-four hours later under drop ether anesthesia. The infant breathed spontaneously. It weighed 6 pounds, 8 ounces, and its general condition appeared good. However, within eighteen hours after birth clonic twitchings of all the extremities, particularly on the left, were noted. These persisted in varying degrees at frequent intervals for about one week. Owing to inability to nurse and difficulty in swallowing, it was fed by gavage for a month. Laboratory studies revealed normal serum calcium and blood sugar levels. The mother's postoperative course was uneventful.

Examination on October 12, 1943, when the infant was slightly over seven months of age, confirmed our impression that the infant was abnormal. This examination performed by a pediatric consultant is reported as follows: "The infant is barely able to hold his head up and makes no effort to sit alone or to grasp objects. His face is not symmetrical, and the right eye is noticeably larger than the left. Both react normally to light. There is a very slight facial weakness on the left. The fontanel is open about 2 cm. He usually keeps both eyes deviated to the right. The whole picture is one of marked mental deficiency with a few physical features which have been mentioned."

CASE 2 (59562).—Age 25. Gravida ii, para i. This patient had been delivered in May, 1942, by cesarean section during the eighth lunar month because of a progressing toxemia of pregnancy. Her present pregnancy had progressed normally with the highest blood pressure reading 126/76 and with no albuminuria. She was admitted for elective cesarean at term on April 18, 1943. She received sodium amytal grains 3 the night before and this was repeated at 7:30 A.M. the morning of operation. At 8:40 A.M. she was given atropine sulfate grain  $\frac{1}{150}$  hypodermically. At this time the blood pressure was 118/78 and the fetal heart rate 160. Caudal anesthesia was started at 8:55 A.M. without difficulty. Eight c.c. of 1½ per cent metycaine solution was injected at 9:03 A.M. This was followed by 30 c.c. at 9:13 A.M. Five minutes after this injection she began to show evidence of vascular collapse. The pulse became thready and rapid. The blood pressure fell to 85/50. Her color became pale and she vomited several times. The fetal heart rate decreased to 60 per minute and very active fetal movements occurred. In approximately fifteen minutes the patient's pulse, color and blood pressure returned to normal and the fetal heart rose to 120 per minute. Satisfactory anesthesia was present and the opera-

tion was performed. During it 20 c.c. of 1½ per cent metycaine were injected at 10:12 A.M. and 10 c.c. at 10:27 A.M. The infant was delivered easily, and weighed 5 pounds 4 ounces. It was slightly cyanotic but the pulse was good. The infant made several respiratory efforts but within a few minutes, it became extremely pale and all evidence of life disappeared in spite of tracheal catheterization and oxygen administration. The patient's postoperative course was uneventful. Necropsy revealed a normal term infant without demonstrable congenital defects. Examination of the cranial cavity demonstrated an edematous area over the lower portion of each of the temporal lobes. The fourth ventricle was filled by a clot of blood. All of the intracranial blood sinuses, especially the occipital sinuses, were distended by fluid and clotted blood.



Fig. 1.—Infant in case XC 66720 at seven weeks.



Fig. 2.—Same infant at seven months.

It is, of course, impossible to demonstrate a direct relationship between these two disastrous results and the obvious periods of anoxia which these infants experienced during intrauterine existence. There is no doubt that the circulatory collapse encountered in both instances was due to the anesthetic agent. Similar episodes have been mentioned by other authors and have consistently been minimized. To our knowledge no similar observations have been made on the fetus during such episodes and there are no reports in the literature of an injuries



effect on the infant following delivery. Windle and Beeker<sup>9</sup> have reported the late effects of intrauterine asphyxia upon the experimental animal in a series of carefully controlled experiments. They are comparable to the experiences we are here reporting. We do not deny that cerebral damage and asphyxia are encountered in infants delivered by cesarean section with other types of anesthesia including even local infiltration. The studies of Adair and Potter<sup>10</sup> and of Potter and Rosenbaum<sup>11</sup> emphasize this possibility. These two cases are included in this report to point out that caudal anesthesia particularly when used for cesarean section may *not* be without any risk for the infant.

No mothers were lost in our series, but we did have an uncorrected fetal mortality of five. One infant was hydrocephalic, two died in utero of unknown cause, and one death occurred neonatally. This latter baby was delivered from below after a forty-eight-hour labor. The delivery was performed after Dührssen's incisions by forceps rotation and extraction. The infant lived forty-eight hours. Post-mortem diagnosis was "atelectasis." The death of the fifth infant was attributed to continuous caudal analgesia. (See Case 2, 59562, page 300.)

The average interval between inception of analgesia and termination of labor was six hours. This period corresponds with that of Hingson and Edwards.<sup>12</sup> In many of our cases we had difficulty in maintaining anesthesia over prolonged periods. In these cases the maximum desirable effect would begin to wane after about six hours. Thereafter larger and more frequent instillations would be required. This phenomenon has been observed by a few other investigators. Greedy<sup>5</sup> has suggested as an explanation the possible refractory action of the nerve roots to the drug after prolonged anesthesia.

It has been our observation that blood loss associated with caudal anesthesia has been definitely less than with other methods of analgesia used in our clinic. Not infrequently the amount of blood escaping from the episiotomy wound exceeds that from the uterus.

### **Comparative Advantages and Disadvantages of the Ureteral Catheter and Malleable Needle Techniques**

Although the same results are obtainable from the catheter and needle techniques, authors are divided as to their preference. This division arises largely from the advantages and objections peculiar to each method. For the sake of refreshment and re-emphasis herewith are listed the pros and cons of the two methods. These have been gathered from the writings of several observers and include those of our own experience.

#### **Advantages of the Needle Technique**

1. The equipment is more easily cleansed and sterilized.
2. Insertion is simpler.
3. Only one piece of apparatus enters the sacral canal, therefore less trauma and less possibility of infection.

4. The tubing-needle connection is more readily assembled than that of the tubing-catheter, and the contact is nearer perfect.

5. The 19 gauge needle will enter a smaller hiatus than the 13 gauge needle used in inserting the catheter.

6. Leakage around the needle through the sacrocoecygeal ligament is less than around the catheter.

TABLE I. SUMMARY OF STUDY

1. Number of cases managed with continuous caudal analgesia:	100
2. Number of cases completely relieved of pain (including 2 cesarean sections):	40 (%)
3. Number of cases partially relieved of pain:	40 (%)
a. Number of cases having a practical but not satisfactory amount of relief	18
b. Number of cases requiring supplementary analgesia Included:	22
(1) Number of cases due to escaping needle	5
(2) Number of cases due to sub-arachnoid injection	1
(3) Cesarean cases	3
4. Number of cases considered as complete failures:	20 (%)
a. Number of failures due to inability to enter hiatus properly	18
b. Number of failures due to reaction of patient (intravenous injection)	2
5. Complications to the mother:	
a. Immediate reactions following injection	2
b. Cases with fall in systolic blood pressure over 20 points	12
c. Infection at site of injection	1
d. Neurologic sequelae	1
e. Broken catheter	0
f. Broken needle	0
6. Complications to the fetus (resulting from marked drop in maternal blood pressure):	2
a. Death from asphyxia in utero	1
b. Permanent cerebral damage from anoxia in utero	1
7. Maternal mortality from continuous caudal analgesia:	0
8. Uncorrected fetal mortality:	5
a. Hydrocephalic	1
b. Intrapartum deaths—cause unknown	2
c. Neonatal deaths	1 (48 hours)
9. Average interval between induction of analgesia and delivery:	6 hours
10. Blood loss less than with other methods employed in our clinic.	

### Disadvantages of the Needle Technique

1. Occasionally the needle slips out.
2. If the patient is obese, the needle frequently misses the hiatus and is inserted over the posterior wall of the sacrum, and the anesthetic is deposited subcutaneously.
3. By scraping the point of the needle over the anterior or posterior wall of the caudal canal, the venous plexus may be pierced. If not checked by aspiration, the anesthetic solution may be injected intravenously with untoward if not fatal results.
4. The needle may pierce the dura, particularly if it is inserted beyond the second sacral foramen, or if the dura should extend abnormally low. Collapse and even death may follow intraspinal injection. This makes checking by aspiration for spinal fluid of utmost importance.
5. The needle breaks more easily than the catheter. For this reason its use is contraindicated in eclampsia and in other types of uncontrollable patient.
6. Anesthesia is more frequently unilateral because of the maintained lateral position of the patient.

### Advantages of the Catheter Technique

1. There is virtually no danger of entering the dura, and much less risk of making an intravenous injection.
2. The catheter can be inserted before active labor begins, that is when the patient has less pain and can cooperate better.
3. The catheter can be introduced farther into the canal, hence it is less likely to be pulled out by movement of the patient.
4. It is of definite choice when dealing with eclampsies and unruly patients.
5. It is easier to ascertain its presence within the sacral canal.
6. If the curve of the sacral canal is exaggerated, the catheter can be passed more readily.
7. The catheter is more yielding than steel, therefore there is less likelihood of trauma.
8. The patient can lie flat on her back and thus equalize the height of the anesthesia on the two sides. She is also freer to move about in bed.

### Disadvantages of the Catheter Technique

1. Greater skill is required for the insertion.
2. The large size of the 13 gauge needle, used in inserting the catheter, usually makes more than one attempt impracticable, because of the trauma and the resulting leaking of the anesthetic fluid, and also, because of the increased possibility of infection.
3. The catheter may be inserted too high and the anesthetizing fluid be deposited at too high a level to involve all the sacral nerves.
4. The catheter may curl within the canal and produce unilateral or incomplete anesthesia.
5. Although danger of puncturing the dura is quite remote, it can be done should the dura be abnormally low (one case in five hundred) or by inserting the needle too high.

All in all the catheter technique appears to be safer and more comfortable for the patient. Also, its use has afforded us more uniform results.

Perhaps it is not so important which technique one adopts as long as he familiarizes himself with the pitfalls of the one he chooses. Greedy<sup>5</sup> has made a suggestion that might compromise the two methods; namely, the use of a smaller catheter threaded through a 16 gauge needle. Block and Rotstein<sup>13</sup> claim to have increased the safety of the method by employing a continuous drip technique, thus avoiding the large injection doses.

In that more than 10,000 labor cases, conducted under continuous caudal anesthesia, have been reported,<sup>12</sup> and for the most part by leading clinicians, a practical attempt now can be made to evaluate the procedure as an acceptable form of childbirth relief. From the thorough analyses made by the various contributors of their respective studies, including those of our own, there has come forth a more or less general agreement upon not only the many merits of the method but upon its several shortcomings as well. To arrive at a just appraisalment one should weigh these one against the other.

### Advantages of Continuous Caudal Analgesia

1. The labor is dramatically painless, the patient being rendered sufficiently comfortable to enjoy reading and normal sleep. She retains all her faculties and has a normal toleration for fluids and food both during and immediately after labor.

At its best the method is truly the answer to (a maiden's prayer). This is well illustrated by the following case:

CASE 1.—S. L., Coleman Hospital, C-8134. Para iii. gravida ii. Age 24. Delivered living twins in 1935, one weighed 3 pounds 14 ounces, the other 4 pounds 14 ounces. In 1936 she contracted pulmonary tuberculosis. In 1937 she was admitted for a rest period at Sunnyside Sanitarium. She was readmitted in 1939 for pneumothorax therapy, phrenicectomy, and a three-stage thoracoplasty, involving eight ribs. Was discharged in 1941 as cured. On September 1, 1942, she was admitted to the Coleman outpatient department for pre-natal supervision.

On March 18, 1943, she entered the hospital in spontaneous labor at term. Continuous caudal was started when the cervix was two fingers dilated and sixty per cent effaced. The total duration of the block, sustained by 75 c.c. of 1.5 per cent of metycaine, was four hours. Although the patient was somewhat nauseated and restless, she was absolutely free from pain. Forty minutes before delivery she went to sleep and while asleep, precipitated a seven-pound four-ounce living female infant. The nurse had to awaken her to inform her that the baby had been born.

2. The method may be of special value where exertion or general anesthesia is contraindicated, e.g., in certain cases of cardiac diseases, pulmonary tuberculosis, pneumonia or upper respiratory infections. (In general these conditions do not contraindicate the use of some of the present-day methods.)

3. The unusual relaxation of the perineal musculature lessens the resistance to the advancing head, and facilitates delivery and breech extraction.

4. It eliminates the need for supplementary anesthesia for normal delivery or repair work.

5. Moulding of the fetal head is almost negligible.

6. The risk of maternal inspiration asphyxia is eliminated. This accident is occasionally associated with narcotic forms of relief.

7. In the majority of cases the labor is shortened and facilitated.

8. Uterine bleeding is minimized.

9. The extra relaxation of the rectal sphincter and the absence of discomfort greatly facilitate rectal examination. The relaxation is so complete that the instructor and student may do the rectal examination simultaneously.

10. The vital mechanisms of the child are not suppressed, and as a result the infant is afforded extra safety. Resuscitation is very rarely indicated. However, since most of the babies breathe and many cry before the shoulders are delivered, one should promptly clear the mouth and nose of mucus as soon as the face passes over the perineum.

11. Because of the freedom from narcosis and absence of moulding of the head, the method is definitely favorable to the premature infant.

*This special protection to the premature infant is perhaps the most outstanding single contribution of continuous caudal anesthesia.* No other method of relief, or even the absence of relief, affords the premature such security. It would appear that prematurity is one of the method's chief indications—providing the maternal blood pressure can be maintained.

12. Post-partum complications are reduced in both incidence and severity.

13. Normal consciousness and orientation eliminate the need for vigilant guarding of the patient against falling out of bed or otherwise injuring herself.

14. At laparotomy the peritoneum is desensitized.

### Disadvantages of Continuous Caudal Analgesia

1. The method is not well adapted to private practice. Not only must the attendant report early in labor to insert the needle or catheter, but he must remain close in attendance throughout the period of anesthesia, not alone to administer the anesthetic but to check carefully the level of the cutaneous anesthesia. Also, a busy obstetrician cannot conduct the procedure in two or more hospitals at the same time. The success of the method really demands a full-time attendant, either a staff man or a resident.

2. Since the method involves invasion of the caudal canal and carries hazardous potentialities, it is a major surgical procedure and should be

conducted only by those fundamentally trained in this specialized form of relief.

3. The method carries an undesirably high percentage of failures—approximately nine per cent in the hands of the more expert.<sup>12</sup>

4. Such contraindications as hypotension, hypertension, eclampsia, placenta previa (increased hemorrhage from cervical relaxation), uterine inertia, acute hemorrhage, sensitivity to the drug, anemia, hysteria, psychotic states, disproportion and certain sacral anomalies should be carefully heeded. The gross frequency of this group detracts from the practicability of the method.

5. Obesity, a small hiatus, or a deformed sacrum not infrequently causes difficulty in inserting the needle.

Unfortunately the sacrum is one of the most anomalous bones in the body, anomalies occurring in ten to fifteen per cent of all individuals. The normal hiatus exists because of the failure of the fusion of the fifth sacral arch. The hiatus may be absent or too small to pass the needle. Again, it may be too large from the failure to the fusion of the arches from the fourth vertebra upward. One case in thirty-five presents complete failure of all sacral arches to fuse. Because of the danger of puncturing the dura this condition contraindicates caudal anesthesia. Also, the dura may be abnormally low, even in cases presenting normal fusion of the arches.

6. Intrauterine manipulations, such as internal versions, are usually unsatisfactory because of the increased tone of the upper uterine segment and the failure to eliminate discomfort from manipulations made through the abdominal wall above the level of the umbilicus.

7. There is a possibility of peripheral nerve damage from a prolonged bathing of the nerve roots with anesthesia agents.<sup>5, 14</sup>

8. There is a risk of spinal infection. Manalan<sup>15</sup> reports a case of staphylococcus meningitis. In their analysis of 10,000 cases of caudal anesthesia Hingson and Edwards<sup>12</sup> report four cases of peridural infection, including one in their own series, which terminated fatally as a peridural abscess.

9. The bladder urge is lost. Not infrequently urine escapes during uterine contractions from pressure of the advancing part, or has to be removed by catheter.

10. The desired anesthetic effect is difficult to maintain over six hours. For this reason it has been found to be most practicable to delay the caudal anesthesia until the pains are two to three minutes apart, the lower segment well effaced, and the cervix at least two centimeters dilated.

Because of this limited duration of efficient anesthesia, prolonged cases may fail to get satisfactory relief near the end of their labor when they really need it most. On the other hand, because of the necessarily postponed administration of the analgesia at the beginning of

labor, many cases, particularly elderly primiparas, are deprived of relief from bona fide discomfort during the early hours of labor.

In cases where this observation applies, continued caudal anesthesia does not meet the concepts of modern obstetrical analgesia.

11. It is exclusively a hospital procedure, and is therefore restricted to approximately sixty per cent (61.2 per cent in 1941<sup>16</sup>) of laboring women. The necessity for a competent anesthetist-obstetrician and special facilities further restricts the use of the method.

12. Although the first stage of labor is shortened and the third is simplified, the second stage is prolonged and necessitates an increased operative interference.

13. Because of the absence of secondary powers and the added fetal embarrassment resulting from the extra prolongation of labor, the method is not suitable in trial labor or borderline disproportion cases.

14. The modern maternal mind cannot revert itself to the prehistoric type sufficiently to accept with warmth and joy the sight of the baby grimed with blood and vernix.

15. In those cases of illegitimacy where the mother is to give up the baby, it is not desirable that the mother see the baby or hear it cry. Nor is the method appropriate in cases of a known monster.

16. The method is not suitable for mothers who prefer to know nothing about their labor. In private practice such patients constitute a goodly number. Also, certain common events and possible accidents during labor and delivery do not invite consciousness of the patient.

17. A majority of patients manifest a drop in blood pressure, varying from a mild to the extreme degree that accompanies fatal cardiovascular collapse.

The larger changes in blood pressure occur in cases where the anesthesia level is at or above the umbilicus, and no doubt result from vasomotor dilatation of the splanchnic vessels and those of the lower extremities. Twelve of our eighty analgized patients presented a systolic drop of more than twenty points. One case in shock reaction exhibited a fall of seventy points.

It is likely that preliminary administration of ephedrine either hypodermically or in the solution would minimize the fall in pressure. However, because of its possible predisposition to uterine relaxation Hingson and Edwards<sup>12</sup> advocate its use only in the event the systolic pressure falls below 90. Some<sup>13</sup> routinely use preoperatively ephedrine sulfate ( $\frac{3}{4}$  gr.) in sections and other abdominal surgery.

That the baby's welfare may be seriously jeopardized by prolonged marked drops in maternal pressure was well demonstrated by our two fetal accidents herein reported. Irving and his associates<sup>17</sup> observed that seventy-five per cent of their fetal distress cases occurred in patients having sustained low pressure, that is, a systolic of less than 90 lasting at least an hour.

18. There is danger of breaking the needle in the caudal canal. Hingson and Edwards,<sup>12</sup> using a malleable German silver needle, report the accident having occurred seven times in their first one hundred and fifty cases. They employed a specially developed malleable steel needle in their next one thousand cases without breakage. However, this type of needle occasionally does break,<sup>14</sup> and Hingson and Edwards recommend not using any one needle over five times.

Breakage of the needle may require incision and even laminectomy for its removal. In one reported case,<sup>13</sup> despite two hours of exploration by an experienced surgeon, the needle never was recovered.

Likewise, but less frequently, a ureteral catheter may break within the caudal canal. Needless to say, the surgical removal of a needle or a piece of catheter greatly complicates a labor.

19. Above all, the method presents a notable mortality for both the mother and the infant. Hingson and Edwards<sup>12</sup> in their ten thousand case report, covering the experiences of fifty-five clinics, record four maternal and two fetal anesthetic deaths. In addition they report in the same article one maternal death and one fetal death in their own series of eleven hundred and fifty cases attributable to the method. In 1920 Zweifel<sup>15</sup> in a series of forty-two hundred single caudal injections reported three maternal deaths attributed to the anesthetic. All three deaths occurred within a few minutes of respiratory failure. Autopsy was obtained on two of them and demonstrated puncture of the dura. Block and Rochberg<sup>3</sup> report three maternal deaths with single injections among the first approximate six hundred cases done in Baltimore. Each of these deaths was likewise attributed to the injection of lethal anesthetic doses into the subarachnoid space. These last fatalities are stated to have occurred despite "strict observance of all ordinary precautions."

These single injection deaths can be reasonably included with those of the continuous technique, in that not only is the same principle involved, but, as is frequently the case, delivery is so imminent that time does not allow for more than the initial injection of the continuous procedure.

It is significant that the ratio of the maternal mortality to the infant loss, resulting from the use of the method, as recorded in the ten thousand case survey made by Hingson and Edwards,<sup>12</sup> and that of their own eleven hundred and fifty cases is as five is to three. This major maternal mortality and the fact that the majority of complications from the method befall the mother make continuous caudal analgesia unique.

The incidence of the maternal loss in the above joint report was 1 death in 2,230 cases. When one combines the figures of the continuous and single injection groups the resulting mortality incidence is found to be 1 maternal death in approximately 1,600 cases (10 in 15,950).

Such rates of loss are too high to be minimized, and should be emphasized, particularly in the light of the success of tried present-day methods of childbirth relief.



Royston<sup>19</sup> reports that since 1936, 7,500 private and ward patients have been delivered in the St. Louis Maternity Hospital under the influence of nembutal-hyoscine analgesia without resulting maternal or infant loss.

Kotz<sup>20</sup> of Washington, D. C., lists one questionable maternal death and one indirect fetal death in a series of 3,000 cases delivered under paraldehyde analgesia. The maternal death case, reported<sup>21</sup> as one of idiosyncrasy to paraldehyde, died of cardiac failure. Although definite anatomic changes were found in the heart at post mortem, the use of the drug was considered a probable factor in precipitating the failure. The infant death was due to a premature separation of the placenta, which resulted from the mother's falling off the table. Kane,<sup>22</sup> formerly of Washington, D. C., in reporting 3,000 private cases delivered under paraldehyde, states he had one maternal death and no fetal deaths attributable to the analgesia. The maternal death resulted from asphyxia following the inspiration of Brussels sprouts.

Gwathmey<sup>23</sup> in 1930 reported 20,000 hospital and home labors conducted under rectal ether analgesia without any resulting maternal or infant mortality. From January 1, 1930, to December 1, 1943, 66,660 mothers were delivered as private and charity patients in the five major Indianapolis hospitals. During this period the modified Gwathmey rectal ether method of analgesia was employed almost to the exclusion of other methods in all five institutions, and a survey shows that at least 40,000 of the labors were conducted under this form of relief. There was but one maternal death attributable to the analgesia in this entire series. This patient died during labor from asphyxia resulting from inspired vomitus. The baby was lost in utero. No other reported or personally known analgesic fetal death occurred in the series.

It is true that all three of the above methods usually require supplementary anesthesia during delivery while caudal anesthesia does not. However, the majority of the serious and minor complications of continuous caudal occur during the analgesia period, that is, during labor, or in other words, during the same period the other methods are employed.

20. Another real handicap of continuous caudal analgesia is its restricted usefulness. In addition to the exclusion of the forty per cent of laboring women who are delivered in homes, there is a very large, if not equal, per cent delivered in those hospitals which are not equipped with the required skill and facilities. Then, too, besides these and those eliminated because of clinical and anatomical reasons, there are the approximate nine per cent of failures. Thus, the method is available only to a minority number of laboring women.

### Conclusions

After reviewing the accumulated findings of capable observers from many leading clinics, the principal forthcoming deduction is that although continuous caudal anesthesia as advocated by Hingson and Edwards is excellent to the degree of captivation in its analgesic achievement throughout both labor and delivery, it is a method fraught with

too many highly dangerous complications to be acceptable except in specially selected cases conducted by specially trained anesthetist-obstetricians.

The degree of risk is such that the method's safety should not be stressed. Fortunately, the relief of childbirth pains does not require so major a procedure. Other efficient methods are simpler and safer.

In final consideration, the appraisalment of continuous caudal analgesia as a practical adjunct to obstetrical anesthesiology may be ascertained best by applying the yardstick expressed by Irving,<sup>17</sup> to wit: "When selecting a method of painless childbirth, safety to the mother and the baby is of primary importance, while the relief of pain should be secondary. If the safety of the mother or child is jeopardized, any method should be condemned regardless of the analgesia obtained."

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## SOME OBSERVATIONS IN THE USE OF CONTINUOUS CAUDAL ANALGESIA\*

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(From the Philadelphia Lying-in Hospital)

SINCE the introduction of continuous caudal analgesia for obstetric cases by Hingson and Edwards in the early part of 1942, we have had the opportunity of observing its use in 927 cases. Several articles concerning the dangers associated with its use have appeared in medical journals and much lay publicity has caused wide discussion between obstetricians and their patients as to its advisability. Premature publicity has been instrumental in antagonizing members of the profession, particularly those who have not given it a fair trial. It seems appropriate that an impartial evaluation of this procedure should be presented to the profession and their attention called to many minor points which have been learned from its use in a rather large series of cases over a period of one and a half years.

It is not the object of this paper to stress the technique of injection, but to present a fair discussion of the use of continuous caudal analgesia from the standpoint of the obstetrician rather than from the viewpoint of the anesthetist.

I, personally, have never in the past promised any woman painless childbirth, and today I do not promise any prenatal patients caudal analgesia, telling them that it depends on the type of labor and other circumstances when they arrive in the labor room. In other words, the patient is made to understand that the type of analgesia or anesthesia to be used must be left to my discretion at the proper time. This obviates any disappointment on the patient's part and impresses the lay person with the fact that caudal analgesia is not a panacea to be used promiscuously for relief of the pains of childbirth.

We feel that the selection of the patient is a most important consideration and the usual contraindications to the use of continuous caudal analgesia are as follows:

1. Gross deformities of the spine, particularly of the sacrum.
2. Tumors which narrow the spinal canal.
3. Local infection around the sacral hiatus.
4. Skin infections such as boils or carbuncles *anywhere* on the body. (A contraindication to be evaluated by the physician in charge.)
5. History of sensitivity to the analgesic agent.
6. Profound anemia, unless supplemented with oxygen inhalation.
7. We have hesitated to use this technique in cases of placenta previa because of the relaxation of the cervix and the possibility of bleeding. This is particularly true if the patient has had any uterine contractions.

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8. Floating head.
9. Patients who have had known syphilis with probable central nervous system lesion.
10. Obese individuals.
11. Dwarfs and midgets, because of low lying dura.
12. Pilonidal cysts.

In addition, we have avoided giving it to patients in labor where the fetus is known to be dead or where monstrosity is diagnosed or suspected. We have hesitated to give it to cases of suspected partial premature separation of the placenta.

Cardiac disease, upper respiratory infections and premature labor are ideal indications for the use of caudal anesthesia. We have also given it to pre-eclamptics and to one or two cases of eclampsia, with excellent results. We have not administered it to any patient in whom we suspected intrauterine fetal death simply because we wished to eliminate any question of this method being the cause of the death. Each patient should be individualized and it is our opinion that seemingly better results are found in the patient of higher mentality. It has been said that "this is the method par excellence for the better classes." When you exclude those in which there is a definite contraindication, together with the certain number of multiparas who are almost ready for delivery when they reach the labor room, we estimate that approximately 62 per cent of all of our patients are suitable. At the Philadelphia Lying-in Hospital there were 964 deliveries since June, 1943. Of this number, 510 were given continuous caudal analgesia, giving a percentage of 52.9. This figure is less than my estimation of 62 per cent because a large number of private patients were delivered during this period by members of the staff who did not use the continuous caudal method. After looking over my own list of private prenatal patients, I conclude that between 60 and 70 per cent are suitable for this type of analgesia. We have tried to evaluate impartially these cases in groups of 100 per cent successful, unsuccessful, or partially successful requiring supplementary pain relief. In the last 553 cases, 92 per cent have been evaluated as 100 per cent successful. The 8 per cent of failures could be attributed to insertion of the needle by inexperienced individuals and anatomical anomalies.

### Time to Start Injection

The most opportune time to start caudal analgesia is when the patient is complaining of pain and is having uterine contractions at 5-minute intervals, of 30 to 40 seconds duration. The cervix should be 3 centimeters dilated and the presenting part engaged or fixed in the pelvis. When the patient is on her side and the fetal head is floating, the forces of the uterine contractions are not always properly directed. Where the head does not descend, the application of a tight binder may be helpful.

We believe it is important that the patient's blood pressure, pulse, fetal heart sounds, amount of dilatation and effacement, and station of the presenting part, should all be checked by the attending obstetrician at this time. This brings up the question as to whether this method is one which should be handled by a skilled anesthetist or by an obstetrician. It is our opinion that the ideal situation is one where the obstetrician and the anesthetist work as a team. Unfortunately, in these trying times, this can be done in only a few clinics. In studying this problem we have been most fortunate in having had the close cooperation of the originators of this method and the mutual understanding between us has resulted in solving many minor details from both the viewpoint of the obstetrician and the anesthetist. We have in our clinic three trained nurse anesthetists who are now perfectly capable of continuing the injections once the proper analgesia level is obtained and to whom we are indebted for many suggestions in the improvement of the technique. However, the attending obstetrician or the medical anesthetist is always easily accessible.

### Technique

When we undertook the study of this procedure, the originators had done 33 cases. Because it was new, and because of potential dangers, we surrounded each patient with all possible safeguards to meet any emergency. There have been only a few instances where they were required, but we strongly advise that the following things be easily obtainable—oxygen, ephedrine, eoramine, plasma, a sterile spinal needle, and a barbiturate. All of our patients are injected while on their side. Because of the discomfort to the patient, the knee-elbow position has been used in only a few instances. When looking for the anatomic landmarks, one must remember that the gluteal cleft is displaced when the patient is on her side.

We have not given any barbiturate intentionally before injection because we did not want to use any combination until several hundred cases had been observed. We believe, however, that it is a good practice to give one of the barbiturates, either by mouth or by hypodermic, in doses of not more than 2 or 3 grains, before starting the injection. A preanesthetic dose of a barbiturate is desirable since it has been proved that such a dose increases the individual's tolerance to the cocaine group of drugs. Also, when barbiturates are used, the patient is quieter and very frequently after the pain is alleviated, sleep is induced. Quietness in the labor and delivery rooms is essential. It is all right to entertain the patient who is having a baby while she is in possession of all of her mental faculties and is suffering no pain, but care should be exercised in choosing the subject of conversation.

If spinal fluid is aspirated after the needle is inserted, it is imperative that this method be discontinued. If blood is obtained, adjustment of

the needle should be made until no further blood can be aspirated. If any difficulty is encountered in placing the needle properly, the patient in all probability should be handled in some other manner. There is no reason for making a pin cushion out of a sacral hiatus.

After the test dose of 8 c.c. has been given, we insist upon waiting a period of 10 minutes to rule out an inadvertent intrathecal injection.

In only 8 per cent of our cases has the blood pressure fallen more than 20 points. If this occurs at any time during the course of labor, 25 milligrams of ephedrine is given and the patient's legs are elevated for one minute. Should the rate of the fetal heart sounds change with the drop in blood pressure, the above procedures are supplemented by inhalation of oxygen. This is followed by an almost immediate return to normal.

When the full amount of the drug is given, all patients do not have the "sciatic sign."

In our clinic we prefer the use of the improved malleable stainless steel caudal needle and since the adoption of its use we have not had any needle break. In indicated cases we have occasionally used the ureteral catheter technique. We have not used the drip method. However, it is not the purpose of this paper to compare the merits or demerits of these three modifications in technique.

Care should be taken to make certain that the drug is thoroughly mixed with the salt solution. If this is not done, a higher per cent solution may be given at first and good analgesia may not be obtained from the remaining solution. After December 1, metycaine will be obtainable in 200 c.c. of  $1\frac{1}{2}$  per cent solution, already mixed in hermetically sealed bottles. We believe this is a definite improvement.

When the injection is given, the syringe should be held in such a manner that the operator's hands do not come in contact with the plunger. As a precautionary measure, after the first injection, 5 per cent sulfathiazole ointment is applied to the skin around the needle and a gauze pad may or may not be strapped over it.

### Management of First Stage of Labor

During this stage, adequate fluids and nourishment should be given to the patient and her morale should be reenforced by regulated conversation, selective reading and radio. Educating our younger men and house staff to the necessity of guarding their conversation in the presence of a patient under the influence of a barbiturate or any other form of sedation, has been a difficult problem. Particularly is this precaution necessary in the presence of a patient who has had caudal and is in possession of all of her mental faculties. It has also been necessary to caution repeatedly those connected with the labor and delivery rooms not to expose any patient unnecessarily. If a patient becomes drowsy from the barbiturate which was given preceding the injection, she should be allowed to sleep, if she so desires. Change of position from one side

to the other not only rests her, but aids in more equalization of distribution of the drug. Care should be taken when changing linen, if it has become soiled by vaginal discharge or fecal material. The bladder should be emptied by catheter, if distended. It has been our experience that with the use of the barbiturates one nurse could never handle more than two patients and actually should only handle one. Since the advent of caudal we find that one nurse with one trained nurse anesthetist, can handle as many as five patients once the injection is started. This we believe to be an ultimate saving in nursing hours per patient.

The patient should be under the constant observation of a trained individual and routine 30-minute checks of blood pressure and fetal heart sounds should be made.

The level of analgesia should be maintained by the injection of 20 c.c. every 40 minutes. If the analgesia level is permitted to fall, it takes additional time and increased dosage to re-establish it.

Some objection has been voiced that more rectal examinations are necessary. To this we do not agree. In fact, we find that fewer are required. Occasionally a multiparous patient, or one in premature labor, will precipitate. When the presenting part appears at the vulvar orifice, there is usually plenty of time to properly prepare the external genitalia for delivery. When the patient is ready for delivery, she may be moved to the delivery room with the needle in situ, or the last injection can be given and the needle removed. When the needle is removed, whether before or after delivery, sulfathiazole ointment and a dressing are re-applied.

We believe that everyone who has used caudal will agree that the first stage of labor is shortened. Our average length of the first stage of labor for a nullipara is about 8 hours.

### Management of Second Stage of Labor

When the cervix has become completely dilated and there is evidence of rectal pressure or perineal bulging, she is placed on the delivery table and the usual preparation of the external genitalia together with emptying of the bladder by catheter is carried out. There unquestionably has been a certain increase in the number of outlet forceps since we have been using caudal. However, we do not object to this because practically all of our patients under any type of analgesia are delivered in this manner.

In delivering with outlet forceps and episiotomy, care should be taken to do the episiotomy at the proper time. Because of the relaxation of the pelvic floor, there is a tendency for one to delay too long in doing the episiotomy.

Very frequently when we apply the forceps an assistant keeps his hand on the patient's abdomen and with each uterine contraction the patient is requested to bear down. In this way the patient practically has a spontaneous delivery, with the forceps simply guiding the head

into the vulvar orifice. It is also true that there are more posterior positions and particularly transverse arrests. The delivery of these cases under this type of analgesia is much simplified because of the marked relaxation. In a transverse arrest we very frequently apply the posterior blade of the forcep and then as the patient bears down with each uterine contraction, anterior rotation of the head is completed with very gentle pressure on the blade of the forcep. A large number can be rotated manually, but if this is not possible, we prefer the application of Luikart's modification of the Tucker-McLane forceps to complete the delivery.

Breech presentations have been delivered spontaneously in almost every instance. We have not attempted decomposition of the breech under caudal except in one instance when we found there was a very marked contraction ring. We believe that breech decomposition and internal podalic version cannot be accomplished under this type of analgesia.

Another point which we consider important is that when the head is about to be born, the chin should be swept over the pelvic floor rather quickly. All of these babies take a breath almost before the head escapes from the vulva and unless one is careful at this stage they may inspire a great deal of mucus and vaginal secretion. These babies all cried almost immediately and none in our series needed resuscitation, except those who inhaled fluid which had to be milked from the trachea.

The psychologic effect on the mother when she hears the baby cry for the first time has been rather unusual and we believe this is an excellent thing, although not particularly essential to good motherhood.

As a rule, we repair episiotomies while waiting for the placenta to separate, although very frequently the placenta separates immediately and is delivered before the episiotomy is repaired. In repairing the episiotomy under these circumstances, one must remember that the perineum is relaxed and it should not be overcorrected.

In a recent communication from Dr. Francis Irving of Syracuse, who has managed 510 cases vaginally and 20 cesarean sections under this procedure, he states that in his series there was a 4 per cent increase of posterior positions. He also called attention to something which we thought was true, but of which we are not yet certain; namely, that the perineal body in these patients at the time of their postnatal examination, seems to be much better than in those patients formerly done under other anesthesia. There is no thinning out and the perineal body is thick and not unlike a nulliparous perineum. Dr. Irving had only one fetal death in over 500 cases.

### Management of Third Stage of Labor

It is important not to manipulate the uterus after the child is delivered, and we do not give any oxytocic drugs until after the placenta has been expelled. We find that the uterine muscle tone is especially good and that the placenta separates very quickly and usually slight



pressure on the fundus of the uterus is all that is necessary to deliver it. Following its expulsion, the oxytocic drugs are injected, preferably in the leg, because the patient does not feel it.

The blood loss is markedly reduced and the average loss in the last 500 cases was 111 c.c. We advise against manipulation of the uterus during this period because we consider overstimulation conducive to more frequent "trapped" placentas. So far we have only had two placentas that had to be removed later. Before the patient leaves the delivery room she is usually given a quarter of a grain of morphine and with it sometimes,  $\frac{1}{150}$  of scopolamine. This seems to be a good plan because by the time the patient returns to her room the effects of the analgesia have worn off and if an episiotomy has been performed, she complains of pain in that area. Because the patients usually return in good condition, not exhausted or tired out, they are probably more hypersensitive to pain at this particular time. Morphine and scopolamine rests them for several hours, following which time food is given to them, if they desire it.

### Cesarean Section

We have performed 66 cesarean sections under continuous caudal analgesia. Two of these cases were unsuccessful because of abnormalities of the sacrum and our inability to insert the needle. I am making a detailed report of our first 50 cesarean sections. In the 66 cesarean operations performed there has been no maternal mortality and no fetal mortality at the time of delivery. All babies, except one, were discharged from the hospital. The one baby was born at  $5\frac{1}{2}$  months gestation of a mother with severe toxemia and weighed  $2\frac{1}{2}$  pounds. It only lived 8 hours.

For the past two and a half years we have not used inhalation anesthesia to any great extent in our section cases, preferring to use fractional spinal, or more recently, caudal analgesia. We have not had sufficient experience with this method to evaluate the difference between spinal and caudal, but we do have a very definite idea that in cesarean section cases these other methods are preferred to inhalation anesthesia. We have not had to supplement caudal with any other method and our average amount of drug used has been 81 c.c. The average blood loss was approximately 100 c.c.

Since the introduction of caudal in our clinic, we have not given oxytocic drugs intravenously. The uterus contracts immediately and it is not necessary to overstimulate it. However, we do give an ampoule of pituitrin and ergotrate intramuscularly after the placenta is delivered. In our series of cesarean section cases there has been no nausea or vomiting and the average drop of blood pressure has been 26 millimeters of mercury. One very constant observation in both vaginal and cesarean section deliveries has been that immediately after the delivery of the baby the blood pressure, if it has dropped at all, will return to normal immediately.

The convalescence of these cesarean section cases has been remarkably smooth. Many of those patients who had been operated upon previously under general anesthesia remarked that the day following operation under caudal they felt as well as they did on the fifth day following their previous section. There has been no persistent nausea, paralytic ileus, or distention. During the puerperal period of both the vaginal and abdominal cases, we have not had to catheterize the patient more often than usual.

### Other Observations

We have had no patient complain of intense pain in the back or legs. The involution of the uterus has been satisfactory and we can see no influence as far as lactation is concerned. We have treated two cases of thrombophlebitis which developed during the puerperal period by caudal injection over a period of four hours, as soon as the diagnosis was established. The results were most dramatic. The patients were relieved immediately of their pain and temperature and swelling subsided in approximately 24 hours. There is possibly a large field for investigation along these lines which we hope to carry out in the very near future.

We have also used this method for puerperal sterilization. The patient is delivered vaginally and while still under the influence of the caudal, she is moved from the delivery room to the operating room and there her Fallopian tubes are resected according to the method of Pomeroy. Although the advisability of puerperal sterilization is a moot question, we believe that if it is done early, the results will be satisfactory. It can be done through a small incision and the patient is able to leave the hospital in the usual time. This is a great saving both from the viewpoint of the patient's economic status and the standpoint of hospital bed capacity.

### Mortality

During the past year and a half, 2 women who had caudal analgesia for their labor have died—one at the Lying-in Hospital and one at the Jefferson Hospital. I cite these two cases, not because the caudal was the cause of the deaths, but because we feel that these cases should be reported in the series.

The first case was a nulliparous woman who was admitted to the hospital with abdominal pain, slight elevation of temperature, and increased leucocyte count. Neither the temperature elevation nor the increased leucocyte count could be accounted for. She was not in labor and the abdominal pain was suspicious of premature separation of the placenta. However, there was not enough to make a diagnosis. Morphine was administered and this gave her temporary relief. Thirty-six hours later her membranes were ruptured accidentally while the patient was being examined vaginally. She went into labor immediately and after the labor was well established, she was injected and the caudal run for just one hour preceding delivery. The child was stillborn and the diagnosis of separation of the placenta was made at the time of delivery. It was

not completely separated, but enough of the circulation had been cut off to account for the baby's death about 20 minutes before delivery. She was returned to the ward in good condition. Six hours later she had a sudden attack of pain in her chest and died within 2 minutes. Autopsy was refused and she was signed out as a case of pulmonary embolism. We do not believe that the caudal contributed to this death.

The second death occurred in a nulliparous colored patient who had not been followed in the prenatal clinic. She came into the hospital in active labor and the caudal was instituted. She had complete pain relief for five hours under caudal and then the level of analgesia was allowed to drop because of the failure of the labor to progress. The patient had a posterior position which remained as such on the perineum for several hours. Five hours after the caudal was discontinued the patient had a convulsion. She was taken to the delivery room and delivered with no form of anesthesia of a vigorous term baby. Eight hours after the caudal had been discontinued, the patient had a series of convulsions which persisted for several hours. It was then determined that she was in a state of anoxemia and was placed in an oxygen tent. A hemoglobin and red cell count at this time revealed 41 per cent with 2,100,000 red blood cells. Eighteen hours after the caudal had been discontinued, the patient died in spite of restorative measures including blood transfusions. Autopsy revealed an ischemia of all visceral organs with a perfectly normal peridural and subarachnoid space. Chemical examination of spinal fluid, urine, heart blood, bile, revealed no evidence of metycaïne.

In 1942 there were delivered at the Philadelphia Lying-in Hospital 2,328 patients with a maternal mortality of 0.11 per cent and an infant mortality of 2.07 per cent. During the period from June 1, 1943, to November 1, 1943, the maternal mortality has been 0.27 per cent and the infant mortality 1.6 per cent.

### Summary

In summarizing and evaluating our experience with continuous caudal analgesia, we believe the most important points to remember are the DON'TS, which are enumerated as follows:

1. Don't think that caudal analgesia is applicable for every woman in labor.
2. Don't give it to a patient where there is any question about her mental make-up or where there is any suggestion or suspicion of the presence of any of the contraindications which have been laid down.
3. Don't start the injection too soon.
4. Don't forget to carefully check the position, station of the presenting part, amount of cervical dilatation, fetal heart tone, pulse, and blood pressure, before the caudal is given.
5. Don't start the injection until you have the patient surrounded by all of the essentials necessary to meet the emergency in case the dura is entered or a blood vessel is penetrated.
6. Don't give the full injection until 10 minutes has elapsed following initial dose of 8 c.c., making sure that the patient moves her feet satisfactorily.

7. Don't talk about other patients' condition in the presence of the woman in labor.

8. Don't forget to check the blood pressure and fetal heart tone at frequent intervals.

9. Don't persist in forcing the needle unless you are absolutely certain about the anatomic landmarks.

10. Don't persist in inserting the needle a second time, if spinal fluid is aspirated.

11. Don't attempt to use this method without the proper equipment.

### Conclusions

After observing continuous caudal analgesia over a period of a year and a half in 927 selected cases, we believe that our experience has been such that we can give a comprehensive evaluation of this method of analgesia.

The most frequent criticism of this procedure is its questionable safety. We are convinced that if the patient is surrounded by proper safeguards and is competently supervised from the standpoint of both anesthesia and obstetrics in a well-staffed maternity, then it is safe for both mother and baby.

In addition to the relief of pain, there are several equally important beneficial factors associated with continuous caudal analgesia which must be considered when evaluating this method. They are, the excellent condition of the baby at the time of birth, the delighted mental attitude of the mother, the minimal blood loss, the easy termination of the third stage of labor, and the return of the patient to her room in good physical condition showing no signs of exhaustion or fatigue.

Although we do not expect the profession at large to accept or adopt this procedure in the near future, we are firmly convinced that carried out under the proper conditions and in the proper surroundings, it is one of the greatest advances known in obstetric practice.

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### Discussion

DR. ROBERT A. HINGSON.—Continuous caudal analgesia from the standpoint of anatomy and physiology is a sound procedure for the following reasons:

(1) There is a functional dissociation between the motor and sensory components of the uterine nerve supply. These two specialized nerve functions have been separated by nature so that several spinal segments intervene between the major pathways initiating uterine contractions and the interpretation of these contractions as visceral pain. The fact that the motor components are found in the upper thoracic areas and the sensory pathways find their synaptic relationships to the central nervous system through the eleventh and twelfth dorsal spinal segments permits the selective regional nerve block to exclude pain and yet not interfere with the contractility of the uterus.

(2) A further dissociation of the innervation of the uterine cervix through the parasympathetic fibers of the second, third and fourth sacral nerve facilitates the regional nerve block of both motor and sensory components to the cervix.

(3) The continuity of the sacral canal with the peridural space permits a regional analgesia of all sensations of labor and delivery without interfering with the natural forces to bring about birth.

(4) The terminal hiatus of the human sacrum presents an ideal point of entrance for medicating the peridural space. The retrogression of the mammalian tail in the phylogenetic development of *homo sapiens* revealed the sacral hiatus as the point of exit of the caudal nerves. This retained vestigial orifice seems ideally suited for the introduction of continuous caudal analgesia.

(5) The close proximity of the sacral canal to the pelvic nerves makes this an excellent approach for producing an extradural nerve block.

The conjugation of metycaine by the liver and reticulo-endothelial system with its rapid elimination through the kidneys permits the fractional administration of this drug to produce prolonged nerve block of the pain impulses without accumulative or deleterious effect on the maternal organism. We have administered as large a dose as 11 grams of metycaine over thirty-three hours, in several patients without complications. This enormous quantity of drug is seldom necessary or advisable, but it illustrates the wide margin of safety in its use.

DR. WILLIAM E. STUDDIFORD.—It is obvious that this method of anesthesia is perfectly harmless as far as the baby is concerned. I am not quite convinced as yet that it is perfectly harmless as far as the mother is concerned. In the recent paper published by Hingson and Edwards in the *Journal of the American Medical Association*, they report four deaths in patients who were cared for in the clinics that they have visited in the past year and a half. This is 0.4 per thousand directly attributable to the anesthetic agent. Anybody will concede that a death occurring during a normal delivery due to an anesthetic agent is a preventable death. In other words, it would never have occurred if the anesthetic agent had not been given.

In the last few days I have reviewed 16,000 deliveries taking place in Bellevue Hospital in the last ten years and found that under our antiquated methods of caring for pain during labor, there were two deaths, or 0.12 per thousand due to anesthesia. In the series under caudal anesthesia there was one death in over 2,500 cases. In the patients there has been one death due to anesthesia in 8,000 cases. So I can hardly believe that this method of anesthesia is less dangerous than the methods we are using at the present time.

DR. BENJAMIN P. WATSON.—At the Sloane Hospital we have done only 25 or 30 cases under caudal anesthesia. In five instances there was complete failure because of inability to enter the canal, possibly due to technical difficulty in some instances and possibly due to anatomical defect in others. In those cases where the technique was properly carried out the results were as Dr. Lull has described.

We have been impressed by the fact that if this method is to be carried out you must have a trained personnel. That was where our difficulty was—we did not have the personnel in the anesthesia department or on the house staff to apply the method as a routine. I think the point is well taken and should be emphasized, that the method is one which can be carried out only under the proper auspices. A warning should be issued that it is not to be used casually by the general practitioner or even by the trained obstetrician unless he has the proper setup.

DR. JAMES R. MILLER.—Since fear has been expressed as to what would happen when this method is used by the untrained obstetrician, might it not be possible for the Public Health Service to ascertain what is going on throughout the country? I am sure that this method is being used in many small hospitals where there are neither trained anesthetists nor obstetricians who are experienced in this method.

DR. GEO. W. KOSMAK.—The procedure so carefully presented by the speaker constitutes a very important suggested addition to our obstetric armamentarium. Until evidence has been presented to the contrary, it may be designated as an American contribution, for apparently it has not been employed elsewhere, at least not to any extent. The enthusiasm of those who have mastered its details and seemingly have overcome its objections, and who are able to point out its satisfactory employment in large series of cases, might prove sufficient to warrant the adoption of the method where the necessary skill and facilities are available.

Therefore, one might be accused of placing an obstruction in the path of progress if one ventures to draw attention by analogy to the old "Stop, Look, and Listen" sign which still marks many of our rural railroad crossings. It seems to me that the time has not come when even enthusiastic reports such as we have had tonight and others with which the medical journals are being flooded, should lead to labeling caudal anesthesia as the ultimate solution of the problem of eliminating the pains of childbirth.

Those of us whose contacts with obstetric practice go back to the beginning of the century, well remember the furor created by the imported "twilight sleep," the Gwathmey rectal analgesia, and later the introduction of the various barbiturates, and the accompanying popular slogan of mothers having babies in their sleep and awaking without any recollection of the horrors of their labor. It would be unwise and perhaps unjust to decry the efforts of those physicians who endeavor to contribute to the effort of making labor easier, but is it wise or just to prospective mothers as a class to make them believe that procedures, such as those described, are essential and that they are free from danger? We are now at the crest of a wave of enthusiasm for what has been made to appear a dramatic procedure, but have we given sufficient attention to its possible shortcomings and aftereffects? Is there a real necessity for subjecting in a routine fashion every parturient to what must be considered, in my belief at least, a major surgical procedure? We gave up chloroform because we became afraid of its dangers to the heart, the liver, etc., yet here we are invading one of the most delicate, sensitive, and easily injured structures of the body with a powerful drug, the reaction to which cannot always be foretold, simply to do away with pain which might be alleviated in less radical fashion. I feel that in most of these reports on caudal anesthesia the failures and shortcomings of the method have not been stressed sufficiently or have been ignored, but sooner or later the objections will come to the fore just as they have in previous procedures. The "don'ts" delineated in Dr. Lull's presentation should be given wide publicity. Even now we read of an increase in the number of posterior positions due to interference with the physiologic activity of the perineal muscles, of an increasing resort to forceps, of shock from an undue fall of blood pressure, of persistent backaches, of paralysis of the lower extremities, and of occasional infections. All of this need not mean an abandonment of the method, but I believe it should remain as a selective and not a routine procedure and that its employment should be limited as to time, to place, and especially to competent personnel. It can never be made applicable for general use and if, as obstetricians we agree on the desirability of giving whatever relief is possible to the woman in labor, we must persist in the search for a method which is more universally applicable and freer from danger.

DR. E. A. ROVENSTINE.—Most anesthetists are not very anxious to discuss obstetrical anesthesia. There are several reasons for this. Since the days of Simpson in Europe and Channing here, obstetricians have been content for the most part, to serve as their own anesthetists. The majority of recent efforts to improve obstetrical anesthesia have been efforts to exclude the anesthetist—as for example, with self administered analgesia, paraldehyde, scopolamine, the barbiturates, etc. The subject presented so ably by Dr. Lull would seem to put the

anesthetist back in the picture of obstetrical anesthesia, although how long he may stay there and how profitable it will be, is highly speculative.

It is difficult for me to discuss this revival of regional anesthesia because my personal experience is limited and I have learned to be wary of early impressions, good or bad. I recall how anxious I was to praise cyclopropane after the first few hundred cases. When my series reached 2,000 I wrote many final statements about its effect. When ten times that number were accumulated in clinics under my direction I was convinced I had the answers. Now that we have 75,000 we are studying the drug intensely.

It is obvious that the merits of continuous caudal anesthesia during parturition are not conclusively proved, although it cannot be argued that the speakers here tonight have not made a good start. We are all sure they will continue.

In its present status, to review it critically it must be pointed out that epidural anesthesia by lumbar injection which achieved the same results as by caudal had a fair trial in surgery but has practically given way to spinal anesthesia because it was determined to be no safer and less convenient.

The low systolic pressure that may accompany such anesthesia if maintained during uterine contractions, with increased intrauterine pressure may result in no effective arterial pressure to the placenta, a circumstance of some consideration.

The total amount of anesthetic drug required for regional anesthesia for prolonged labor will be observed with concern by many pharmacologists, especially since no soporific drugs are given to protect against toxic reactions. The role of the liver which must detoxify these drugs is not assessed. We may also assume they reach fetal circulation as do other anesthetics put in the maternal blood stream, and we do not know what happens to them in the fetus. Finally, we have no accepted experimental evidence as to what happens to nerves partly paralyzed for a prolonged time.

DR. WILLIAM H. CARY.—I would like to ask Dr. Lull how this continuous caudal anesthesia can be adjusted to patients with an unusually long first stage of labor, or does he feel that it shortens the first stage sufficiently so that this is no longer a problem?

DR. I. C. RUBIN.—The thing I have not heard stressed and which I would like Dr. Lull to talk about if he can, is not the mortality, which we know. What I would like to know is what are the sequelae. If Dr. Lull will tell us that, he will have satisfied all of our questions.

DR. HARRY ARANOW.—I have had extensive experience in the administration of 'twilight sleep' during the days of its very enthusiastic reception. A few years later, I wrote an article entitled "A Post Mortem on Twilight Sleep" in which I stated that the method had many merits but that the general publicity it received had killed it with the medical profession.

What I am afraid of is that the same thing may happen to the method described here this evening. I know personally that it is now being used in some small institutions under unfavorable circumstances.

DR. LULL (closing).—In reply to Dr. Studdiford's citation of statistics, I remember my old friend, Dr. John Chalmers da Costa saying "Statistics never lie, but statisticians can." The paper reporting 10,000 patients handled by continuous caudal anesthesia was published with the deliberate idea that the truth should be known about this method when handled by a large number of persons. Of the four deaths occurring in that series, the first resulted when the patient was given the solution by the continuous drip method and the attending intern and nurse left the patient alone. When they returned they found the woman

was dead. The second case was handled by an osteopath. The third case was a serious cardiac patient who was in decompensation and would have died anyway. The fourth death was due to infection, an infection traced to contamination of the solution and the syringe. There is a great possibility that infection may be introduced into the sacral canal and although I fear this less as our experience with this method increases, I never lose sight of the fact that everything possible must be done to prevent such infection occurring.

Dr. Davies' discussion of the anatomy is very apropos and we found, as he did, that there are many more sacral anomalies in the male than in the female. Dr. Trotter, of St. Louis, will very shortly report a careful study of some 10,000 dissected sacra. Incidentally, we studied the sacrum of "One-Punch Annie." This female lived in the early nineties, was 6 feet, 7 inches tall, and weighed 260 pounds. She went about the country offering to fight any gentleman in the audience, and it was said she had to hit her opponent only once and he went down and out.

I consider Dr. Watson's remarks extremely fair. What I attempted to tell you tonight is that you cannot, you must not, and you should not use this method unless you have the proper facilities and setup for its use. We have been able to carry out our study only because we have had the aid of three very skillful nurse anesthetists, and the cooperation of Dr. Hingson and Dr. Edwards.

In reply to Dr. Kosmak's remarks, I would like to call his attention to the fact that we have tried to stress at all times not only the necessity of having this method used only in selected cases, but also by specially trained individuals. I well remember coming here twelve or fourteen years ago when the barbiturates were first being used. There was plenty of adverse criticism at that time, but we still use them. Irrespective of what some men think, I believe that in this age women are entitled to a certain amount of relief of pain during childbirth, if this can be accomplished by the use of a safe method, and I wish again to call your attention to the other benefits derived from continuous caudal anesthesia in addition to the pain relief. Babies do not require resuscitation, there is minimal blood loss, and an easy third stage of labor, together with the patient returning to her room not exhausted or mentally confused by the use of drugs or anesthesia.

A word should be said in regard to Dr. Miller's question relative to small hospitals. Since June of this year, we have been training five men a week in this technique so that by this time approximately 160 doctors practicing in practically every state in the Union have had special training. We realized that this method was going to be tried by these men who are practicing at distant points and felt that the sooner a certain number of them could have the benefit of the expert teaching of Drs. Hingson and Edwards, the better off the patients would be. There is no way that we can control its use throughout the country so that it seems only logical to carry on an educational program. If some doctor out in the sticks wants to try it and a patient dies, that does not mean that the method itself should be condemned.

In regard to Dr. Cary's question, there is no doubt in our minds from our observations, that the first stage of labor is unquestionably shortened. One of the most frequent mistakes made in using continuous caudal analgesia is that it is given too soon. We allow our patients to have at least one hour of fairly good labor before starting the injection. It has been our observation that the contractions of the uterus increase, decrease, or remain the same, just as they do in any labor with or without analgesia. On several occasions, if we thought the patient was in for a long labor, we have carried her along for several hours under barbiturates and then finished the labor under caudal. In other cases where we felt the labor was not progressing satisfactorily under the caudal analgesia,



we have withdrawn it and used other methods for the relief of pain during labor and delivery.

In our study we were probably most interested in morbidity as we did not know what to expect following this procedure. I can truthfully say that in our series we had no untoward sequelae and our morbidity rate was the same in those who had this form of analgesia as in those who did not have it.

One of the chief criticisms has been that the patients given continuous caudal analgesia require catheterization for days following delivery. This is not true. A patient, no matter what form of analgesia is used, if allowed to have a distended bladder for a long period of time during labor, will have to be catheterized. It is therefore important that the bladder be emptied by catheter during the course of labor and not allowed to become distended.

In closing may I thank you for your kind reception and again tell you that this is simply a report of what we have observed. We studied this method from many angles before we tried it and we believe that there are still many problems which should be studied more carefully. At the present time our pediatric department is endeavoring to ascertain whether or not any of the metycaine gets to the baby. We have arrived at a point, however, where we feel that under the conditions laid down, this is a safe procedure and shall continue to evaluate it further. At the present time I think we can report sufficient progress to say that continuous caudal analgesia is here to stay.

# THE RESIDUAL EFFECT OF PROLONGED CAUDAL ANESTHESIA UPON THE NEUROMUSCULAR SYSTEM IN DOGS

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LITTLE evidence of lower motor or sensory nerve degeneration has been reported from single injections of cocaine derivatives, but the possibility of such damage from their prolonged application has not been ruled out. In view of the introduction of continuous nerve block anesthesia, both spinal (subarachnoid) and caudal (epidural), such an investigation is of practical significance. A few cases of transient paresthesia and leg pains following continuous caudal anesthesia for labor have suggested the possibility of nerve impairment.

The problem as outlined for this experiment was (1) to administer epidural anesthesia to the dog via the caudal canal; (2) to determine if nerve degeneration (motor) may result from continuous epidural anesthesia as ascertained by chronaxie determinations and observations of the behavior of the dogs; (3) to study the effects of epidural anesthesia upon the dog.

The anesthetic agent was placed<sup>1</sup> in the epidural space through a needle entering the canal between the bifid spinous processes of the lower sacral vertebrae. The needles employed were 20 gauge, 3½-inch with stylette. Verification of the proper placement of the needle was at first made by dissection. It was observed that the patellar reflex was quickly abolished after injection within the epidural space while injection outside the canal left the reflexes intact. The first dog which had been injected with 1½ per cent metycaine tinted with methylene blue died of respiratory paralysis. Removal of the laminae of the spinal vertebrae revealed staining of the epidural fat up to the midcervical region.

Dogs ranging in weight from 7.75 kg. to 20.5 kg. and of both sexes were anesthetized with sodium pentobarbital given intravenously in dosage of 35 mg. per kg. of body weight at first and later 25 mg. per kg. This anesthesia provided the required immobility necessary for inserting the caudal needle. The effect of barbiturate anesthesia<sup>2</sup> in this quantity did not appreciably alter the normal chronaxie measurements though the deep reflex (patellar) was definitely enhanced.

Metycaine was chosen as recommended by Hingson and Edwards<sup>1-3</sup> for continuous caudal anesthesia in the parturient. Eight animals were given metycaine 1½ per cent in saline in the proportion of 30 c.c. to 70 kg. of body weight comparable to the dosage in the human being. Four animals were given 5 per cent solution in saline but in smaller volume in view of previous experience of respiratory failure. Five

animals received injections of  $7\frac{1}{2}$  per cent in saline solution also in smaller quantity. The reason for this increased strength of solution was to estimate a tolerance or margin of safety.

Of the animals receiving metycaine  $1\frac{1}{2}$  per cent, two died and six survived. The deaths were ascribable to respiratory failure, presumably due to blocking of the roots of the intercostal and phrenic nerves. The muscles first depressed were the intercostals, next the diaphragm, after which could still be seen the action of accessory respiratory muscles in the head for a short time. Five animals received the 5 per cent solution with the loss of two under similar circumstances. Five animals were given  $7\frac{1}{2}$  per cent strength of which two failed to survive. The majority of the deaths occurred in the first half of the series before the appropriate dosage had been ascertained.

The determinations of normal chronaxie were made during the period of anesthesia. Subsequent determinations were made at the end of one and two weeks upon the same muscle groups; namely, the posterior muscles of the legs innervated by branches of the sciatic nerve. Barbiturate anesthesia was administered for each chronaxie test to secure adequate relaxation for reading the minimal muscle twitches. The weekly intervals were chosen because a one-week interval after nerve damage will give a considerably prolonged chronaxie time as shown experimentally.<sup>4</sup> A few animals of docile nature were administered the caudal block in the absence of barbiturate general anesthetic. In these the chronaxie readings were little if any different from the others.

After a few trials the needle was placed in the caudal canal with little trouble. Upon experimentation it was found that  $1\frac{1}{2}$  per cent metycaine in saline could be injected 0.43 c.c. per kg. of body weight at 90- to 120-minute intervals, 5 per cent metycaine in saline could be injected 0.333 c.c. per kg. of body weight at 120-minute intervals, and that the  $7\frac{1}{2}$  per cent solution in saline could be used 0.18 c.c. per kg. also at 120-minute intervals. Increased frequency of injection resulted in too high and fatal anesthesia. Increased volume also caused respiratory failure. Speed of injection apparently did not modify the results.

These concentrations with the amounts given at the specified intervals produced the desired amount of caudal block as evidenced by lack of patellar reflex, lack of flexion response to painful stimuli, lack of movements when the rest of the body was shivering in the anesthetized, or with voluntary motion in the unanesthetized. The minimum duration of the anesthesia was approximately 8 hours, and the maximum was  $9\frac{1}{2}$  hours.

There was an average lowering of the blood pressure of 23 mm. Hg systolic and 24 mm. Hg diastolic in the seven animals studied. The method of determining blood pressure was by auscultation, using a pneumatic cuff on the upper part of the forelimb.<sup>5</sup>

TABLE I. DOGS WHICH SURVIVED

NO.	SEX	KG. WT.	STRENGTH OF SOLUTION	VOLUME OF SOLUTION	TIME BETWEEN FIRST AND LAST INJECTION	MG. OF MET. IN CANAL	MG. OF MET. PER KG. WT.	NO. OF DOSES	CHRONAXIE BEFORE	CHRONAXIE AFTER
2	M	24.50	1½%	10.0 c.c.	Not continuous	150	6.25	1	0.3	0.2
4	F	15.00	1½%	39.0 c.c.	7 hrs. 50 min.	585	39.00	6	0.2	0.3
6	M	9.50	5%	14.0 c.c.	7 hrs. 45 min.	700	73.70	5	0.2	*4.0, 10.0, 0.3
8	F	12.00		Not in the canal						
10	M	12.50	5%	14.0 c.c.	7 hrs. 54 min.	700	56.00	5	0.2	0.2
11	M	7.75	5%	15.9 c.c.	8 hrs. 30 min.	795	102.50	6	0.2	0.2
12	F	13.50	1½%	34.8 c.c.	8 hrs. 15 min.	522	38.60	6	0.2	0.4
13	M	8.00	1½%	17.5 c.c.	6 hrs. 2 min.	262	32.80	5	0.2	0.3
14	M	9.20	1½%	15.6 c.c.	6 hrs. 13 min.	234	25.50	4	0.2	0.3
15	M	20.50	7½%	17.7 c.c.	6 hrs. 32 min.	1328	64.70	4	0.3	0.2
17	M	11.00	7½%	13.0 c.c.	7 hrs. 30 min.	976	88.70	6	0.2	0.3
18	F	15.25	7½%	19.0 c.c.	6 hrs. 40 min.	1425	93.50	6	0.3	0.2

## DOGS WHICH DIED

1	M	24.50	1½%	20.0 c.c.	1 hr.	300	12.22	2	Not significant	
3	F	15.50	1½%	19.5 c.c.	3 hrs. 50 min.	292	18.80	3		
5	M	21.50	5%	18.4 c.c.	40 min.	920	42.70	2		
7	F	9.00	5%	6.0 c.c.	1 hr. 36 min.	300	33.40	2		
9	F	12.00	7½%	7.7 c.c.	Immediately	577	48.00	1		
16	M	13.00	7½%	9.0 c.c.	1 hr. 45 min.	675	51.90	3		

\*One, two, and four weeks respectively.

Nembutal anesthesia prevented convulsions in the group receiving metyeaine 7½ per cent. The three dogs given caudal block with this strength metyeaine who had no barbiturate all manifested convulsions.

In all cases the normal chronaxie time ranged from 0.1 to 0.3 sigma (1 sigma = 0.001 second). In only one dog (No. 6) was there any definite change in the reading, which increased from 0.2 sigma to 4.0 sigma at the end of a week and to 10.0 sigma after two weeks. The museular movements were subnormal. At the end of one month the chronaxie had returned to normal as had also the musele coordination and strength. This dog was injected with metyeaine 5 per cent in saline. In all other dogs there was no museular weakness. The factor of trauma to the nerve trunks from the needle in this dog is not ruled out. The needles were found on dissection to lie in contact with the lower spinal nerve roots and might well have produced local trauma in this case.

The high incidence of mortality in the animal cannot be explained entirely by the increased strengths of solution used in this experiment. Two dogs died from each of the three different concentrations employed. In view of the high level of penetration of the blue dye, as detected by dissection, it would appear that volumes of solution comparable to the dosage in human beings ascend to higher levels in the animal. A relatively smaller epidural space in the animal might well explain this phenomenon.

### Summary and Conclusions

1. Dogs were given prolonged caudal anesthesia with 1½ per cent, 5 per cent, and 7½ per cent solutions of metyeaine in normal saline with little or no residual damage to neuromuseular mechanism.
2. Sodium pentobarbital apparently inhibited convulsions in the group of dogs given 7½ per cent metyeaine.
3. Height of anesthesia depended on frequency of injection, strength, and volume of solution.
4. Blood pressures were uniformly diminished on administration of the caudal block in seven animals.
5. Deaths under the anesthesia were due to respiratory failure.

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## FURTHER STUDIES WITH CONTINUOUS DRIP CAUDAL ANESTHESIA\*

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THE continuous drip method<sup>1</sup> of caudal anesthesia, a modification of the original technique of Edwards and Hingsou, was first published because we found that it permitted a more even anesthesia and eliminated the danger of large rapidly injected doses at all times during the course of labor. Further studies with this method produced the "saline rate test" to detect inadvertent puncture of the dura and the "palm test" to determine subcutaneous insertion of the needle.<sup>2</sup> As a result of additional clinical experimentation, this method has been somewhat modified, and it is the purpose of this paper to present these changes and to discuss certain controversial steps in the procedure.

In our previous papers, a 1 per cent solution of procaine was advised. This was administered at the rate of 15 to 20 drops per minute. Results were satisfactory, but in a few cases there was a rather profound drop in blood pressure, accompanied by pallor, feeble pulse, and thirst. These patients invariably showed a high level of cutaneous anesthesia. Since the level of anesthesia depends on two factors: the rapidity of administration and the volume introduced, we found, by using a 2 per cent solution 8 to 12 drops per minute, the anesthetic can be kept more easily at the desired level, and the tendency for shock-like symptoms to occur is greatly diminished. The same number of milligrams per hour is given, but in half the volume and at a slower rate.

The malleable spinal needle previously suggested is no longer employed. A new needle (Fig. 1), patterned after that of Edwards and Hingsou, has proved more successful. This 17 gauge, hubless needle is far less likely to rotate or to be pushed through the dura by movement of the patient. Unlike a 19 gauge needle, this needle has sufficient body to resist breaking provided that it is not grossly overused. It has been used in 100 cases without complications. The improved quality of the needles has eliminated the principal advantage of the catheter method, a technique which undoubtedly is more traumatic and possibly more likely to produce infection because of the difficulty in sterilization, the excessive manipulation, and the increased trauma.

The author has recently devised another needle (Fig. 2) which unfortunately has not yet received sufficient use to evaluate fully. It is a 3 inch, 17 gauge malleable needle with the Hingsou and Edwards type of hub. The point of the needle is closed and blunted. There are two small side holes almost  $\frac{1}{2}$  cm. from the tip. The purpose of this

\*The Abbott Laboratories supplied the procaine and equipment. Becton and Dickinson aided the development of the needles.

needle is to increase the safety of the indwelling needle as it is believed that the blunted tip will push rather than pierce the dura if the patient were to make pressure on the needle. The needle sometimes needs preliminary skin boring similar to a technique described by Lundy. The anesthetic flows easily through the lateral holes and is distributed more equally to both sides of the caudal canal.

It must be emphasized at this point that only 17 gauge needles should be used for this method. The previously described saline rate test to differentiate between a caudal and spinal injection depends on certain fixed conditions, and any deviation will, of necessity, invalidate the established criteria. For example, markedly different rates of flow can be obtained in a given patient by substituting a 19 gauge or a 15 gauge needle. The 17 gauge needle has been found most satisfactory

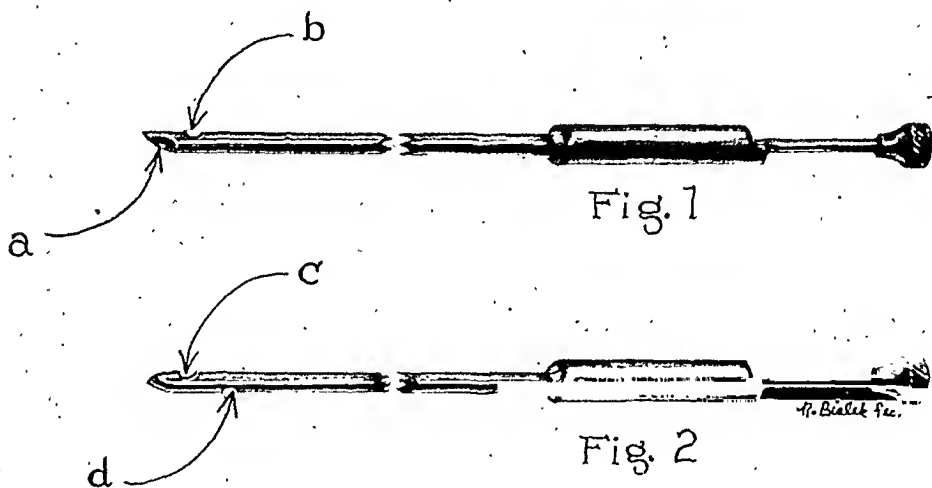


Fig. 1.—Three-inch 17 gauge malleable needle with Hingson hub and side opening.

Fig. 2.—Three-inch 17 gauge malleable needle with closed, blunted tip and two side openings.

as it permits a continuous drip for long labors, yet it produces the clearest differentiation between the caudal and spinal rates. The 19 gauge needle often did not allow passage of sufficient drug by gravity to maintain anesthesia, and a 15 gauge needle was not only found to be too traumatic, but it produced a caudal rate so rapid that it was easily confused with the spinal rate.

The palm test was probably not given sufficient emphasis in our original description since it has proved to be 100 per cent accurate in eliminating the most frequent cause of unsuccessful analgesia—namely, injection superficial to the sacrum by an operator unaware of his error. In all other methods, this error is more possible as it depends on palpating the subcutaneous infiltration, a procedure which is often difficult, especially in the obese patient. The palm test is visual and re-

moves all doubt in the mind of the operator. We have encountered on several occasions, cases in which no pulsation or bulge could be palpated, yet the needle was improperly inserted, and this could only be determined by the palm test. These findings were repeatedly checked by x-ray and without exception, the test was substantiated. Since its adoption, there have been no failures except in three instances when we were unable to enter the caudal canal for anatomical reasons. The author feels that this almost infallible test is sufficient reason in itself for using the continuous drip method.

### Results

One hundred fifty pelvic deliveries and 35 surgical procedures have been performed under continuous drip caudal anesthesia. These cases are mostly from the obstetric service of Sinai Hospital, Baltimore, Md., plus some from private practice. They include the previously reported series.<sup>2</sup>

There were no maternal mortalities in this series, and none of the four fetal deaths were due to the anesthetic; a finding which was confirmed at the autopsy table. Almost every type of pelvic delivery was successfully performed. We found, like many other authors,<sup>3-5</sup> a shortened, almost painless first stage and a delivery, accomplished without inhalation anesthesia, characterized by decreased blood loss and absence of fetal distress.

Since instituting the saline rate test, there have been no cases of inadvertent spinal injection. All cases which received the anesthetic first satisfied our criteria for a caudal rate of flow with saline. Although dural penetration could not be proved, the anesthesia was withheld in 3 other cases because this rate was exceeded.

Thirty-five surgical procedures, including low cervical, classical and Porro cesarean sections, hysterotomy, hemorrhoidectomy, anterior and posterior colporrhaphy, tubal sterilization, appendectomy, salpingectomy, oophorectomy, and curettage, were performed under this method with complete surgical anesthesia and no serious complications.

Seventeen cesarean sections were performed without maternal or fetal death. Lahmann and Mietus<sup>6</sup> recently reported 48 cesarean sections under single injection caudal anesthesia. We have obtained similar favorable results. A complete abdominal anesthesia is produced with minimum risk to mother and baby. The objections they raise are due to the single injection technique, and these can be eliminated with continuous drip anesthesia. They reported several cases in which the anesthesia wore off before the operation was completed. Obviously, this does not occur with a continuous technique. They also had three failures which they attributed to the fact that they did not realize that the solution was being injected subcutaneously. The error can easily be eliminated with the palm test of the continuous drip method. The only apparent real objection to this method is the slowness with which satisfactory anesthesia develops. With our method about 30 to 40 minutes must elapse before the surgeon may proceed. Except in cases of emergency, this interval offers no real obstacle.

### Summary

One hundred fifty pelvic deliveries and 35 surgical procedures, including 17 cesarean sections, were performed under continuous drip



caudal anesthesia. Results were highly satisfactory, especially in the latter part of the series where certain modifications of the previously reported technique have reduced complications to a minimum. Breaking of the indwelling needle has become a remote possibility with the new types that are now available. Since instituting the saline rate test, no inadvertent spinal administration has occurred. The newly advised dosage has reduced reactions since the smaller volume confines the anesthesia to lower levels. The palm test has eliminated the possibility of complete failure due to subcutaneous injection.

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## PARAVERTEBRAL SYMPATHETIC NERVE BLOCK, A METHOD FOR THE SAFE AND PAINLESS CONDUCT OF LABOR

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WITH the advent of regional anesthesia a great boon was given to the field of obstetrics. The first real advance toward an understanding of the sensory pathways from the uterus was made by Cotte in 1925 when he introduced his operation for the relief of dysmenorrhea by section of the presacral nerve plexus. Study of patients who had undergone this operation, revealed that all of them had decreased pain with subsequent childbearing, and most, indeed, had absolutely none. The location of this plexus is such that blocking it during labor is a mechanical impossibility, and the operation is too extensive to warrant frequent use.

Dellepiane and Badiuo in 1927 worked on the theory that the nerves of the presacral plexus were in communication with the hypogastric plexus. They developed a somewhat complicated and intricate technique for blocking the hypogastric plexus in patients during labor and were successful in abolishing the pain of uterine contractions, but their method was too difficult and entailed not a little danger so its routine use has seemed impracticable.

Cosgrove in 1932 published a series of over one thousand cases in which spinal anesthesia was used for final delivery, as well as the end of the first stage of labor. The dangers of spinal anesthesia in a pregnant woman are now well recognized, and in addition, its use to control the pain of labor is ill advised due to the fact that it slows, and frequently stops the progress of labor.

Cleland in 1933 published an excellent paper with the first conclusive evidence of the innervation of the uterus. By means of animal experimentation, and clinical observation upon the referred pain of patients during labor, he deduced that the nerve pathways of the uterus, as far as sensory stimuli were concerned, came through T-11 and T-12. He substantiated this by blocking the dorsal nerve roots and their corresponding rami communicantes, and successfully abolished the pain of uterine contractions. He carried a few such patients through labor in this manner, and delivered them with a low caudal anesthesia.

Hingson and Edwards in 1943, first published their work on continuous caudal anesthesia which is, in substance, a roundabout method of accomplishing the same type of block as that achieved by Cleland in 1933, except that they used only one needle puncture and carried the anesthesia as long as desired by repeated injections.

Schumacker, Hellman and Manahan in 1943 published a series of cases of patients in labor in which the pain was controlled by a single paravertebral sympathetic nerve block. They were unimpressed with its value,

due to the relatively short duration of anesthesia. The author had the privilege of observing the first of the cases reported by Manahan, and felt that the method deserved further study, and hence has carried forward his investigations which are now reported.

The results sought in this work are for the complete relief of labor pain without slowing or impeding the progress of labor, with safety to both mother and child, with uncomplicated means of delivery, and with no undesirable sequela. It was my thought that temporary suppression of painful stimuli transmitted by way of the paravertebral sympathetic chain could be repeated whenever and as often as necessary, and that the method of block should be simplified to the greatest possible extent.

### Technique

The instruments and equipment have been reduced to the simplest items. A tray is prepared which contains the necessary equipment, which can be easily sterilized and covered with a sterile towel. The tray needs only the following: Two folded sterile towels for draping, one large Luer Lok syringe, one No. 24 gauge hypodermic needle, two No. 20 or 22 gauge spinal puncture needles, five or six gauze sponges for cleaning the skin, one clamp suitable for holding the sponges, and a sterile bottle of one per cent procaine in saline solution containing at least 75 cubic centimeters of the solution. A No. 18 gauge needle is helpful for transferring the anesthetic agent from the bottle to the syringe.

Patients were treated without preference, both multipara and primipara, as they came to the delivery floor in so far as they could be followed with adequate notes and observation. Definite criteria for labor were established as follows: The pains were established as regular, of five- to seven-minute intervals and normal duration. The cervix was effaced and partially dilated. The blocks were given through the interspace between L-1 and L-2, and were repeated whenever necessary as evidenced by returning of subjective pain. A perineal pudendal block was used for the actual delivery of the baby. Accessory medication by mouth was not used until twenty cases had been delivered using only paravertebral and perineal blocks. It was then found to be advantageous to use a small dose of sodium pentobarbital.

To obviate perineal pain completely, it is necessary to block not only the pudendal nerve but also the ilio-inguinals. To avoid the necessity of blocking the ilio-inguinals, two or three breaths of nitrous oxide and oxygen are given with the last one or two pains to control the pain due to stretching of the labia.

Solutions of anesthetic agents tried included 1 per cent procaine in saline, 2 per cent procaine in saline, 1 per cent procaine in oil, and metycaine. Of these, 1 per cent procaine in saline gave equally good results, and as it is far less toxic, it consequently was the anesthetic agent of choice.

Episiotomy was used in all deliveries. Spontaneous delivery was the rule although no hesitation was felt in the use of forceps when indicated.

Since the nerve fibers carrying pain stimuli from the uterus enter the cord at T-11 and T-12, injections must be made below this level in order to be effectual. These fibers lie lateral to the vertebral column

in the upper lumbar region but, in order to form the sacral plexus, they curve over and come to lie on the ventral side of the veterbrae column in the lower lumbar and sacral regions. Consequently, injections through the lower lumbar levels are apt to be unsatisfactory because of the increasing difficulty of placing the anesthetic agent in the optimum position. Therefore the interspace between L-1 and L-2 was chosen as the logical and best level for injecting the sympathetic chain although if this is unsuitable because of vascular or skeletal abnormality, the next interspace, between L-2 and L-3, can be used. However, if bleeding is encountered with the insertion of the needle it is best to consider the case unsuited for this means of anesthesia.

The actual method of inserting the needles and anesthetic agent has been simplified and is carried out as follows: The patient is placed in a sitting position on the side of the bed, bent forward as much as the pregnant uterus will allow. The back is cleaned with a suitable antiseptic agent for the skin, and sterile rubber gloves are worn by the operator. The first lumbar spine is identified, and a wheal raise in the skin 5 centimeters lateral to each side. Standard 20 gauge lumbar puncture needles are then introduced through the wheals at an angle of about 60 degrees with the skin, slanting inward. No further injection need be made for the insertion of the needle other than the skin wheal. The needle passes between the transverse processes of the first and second lumbar vertebra, and as the point is felt against the body of the vertebral column, it is then straightened to an angle approaching 90 degrees with the skin, and passed beside the body of the vertebra a distance of approximately  $1\frac{1}{2}$  centimeters further. If the needle strikes a transverse process, it can be routed around this by going above it with but little difficulty, fortunately, this is a relatively unusual occurrence. Needles are placed on each side before an injection is done, careful aspiration with the bevel of the needle in all four directions is done before any solution is injected. The needles are inserted to a depth governed by the depth of the body of the vertebra. This may be eight, ten, or twelve centimeters depending upon the patient but as this thickness is muscle and subcutaneous fat there is no danger of puncturing important structures. By placing the needles just above the transverse processes, one avoids the vessels which lie on their lower surfaces and likewise avoids striking the somatic nerve trunks as they leave the spine. Thirty cubic centimeters of one per cent procaine in saline is then injected at each of these two sites. The needles are then withdrawn, and the injection sites sealed with flexible collodian. Aspiration of blood indicating a rich capillary plexus or the puncture of small vessels is a contraindication for injection. Other contraindications will be dealt with later in the paper. The entire time necessary for the injection, from the time the patient is prepared until she can again lie down, is seldom over five or six minutes, and the pain of the uterine contractions is abolished immediately.

Perineal pudendal blocks can be effected by any of several methods. The author prefers a long small gauge needle. Only one puncture is made and this at the fourchette, the needle being maneuvered without completely removing it. Injections are made laterally where the pudendal nerve emerges from under the gluteal muscle and also in Alcock's canal. It was likewise found advantageous to infiltrate the labia majora with a small amount of procaine.

## Results

In all, seventy cases have been treated in this way; forty-six of which were primiparas and twenty-four multiparas. They were given as many injections as each required. Many patients arrived at the hospital with labor definitely established, and the cervix dilated sometimes several centimeters. Consequently, the majority of these patients required only one block; others were given multiple injections as necessary, as shown by Table I.

TABLE I. SHOWING THE INCIDENCE OF MULTIPLE INJECTIONS IN PATIENTS REQUIRING MORE THAN ONE

NUMBER OF INJECTIONS	PRIMIPARA	MULTIPARA
2	25	22
3	15	1
4	4	1
5	2	0

In the primipara group, the average length of anesthesia for each individual nerve block was one hour and thirty minutes. Many of the blocks lasted through delivery, and therefore, an accurate determination of their length of action is not possible. The same is true of multiparas, and the average length of anesthesia in those injections, where it could be measured, was one hour and twenty-four minutes. In all cases there was immediate relief of pain although the uterine contractions were of the same frequency and duration, and the quality, as determined by inspection and palpation, remained unchanged. Fetal heart tones were carefully followed throughout, and in all cases remained normal.

The duration of labor varied over a wide range. One case was prolonged, lasting thirty-six hours, and two cases were under three hours. None were precipitous. In the primiparous group, the average length of labor was twelve hours and thirty minutes, divided into a first stage of eleven hours and eighteen minutes; second stage, one hour and three minutes; third stage, nine minutes. In the multiparous group, the average of all cases was ten hours and thirty-two minutes for total duration; nine hours and fifty-four minutes, first stage; twenty-seven and one-half minutes, second stage; and ten and one-half minutes, third stage. These figures show to better advantage if the dilatation, when the blocks were first started, is taken and the time necessary for complete dilatation to occur is considered, as many of these cases had been in labor for some time at home before coming to the hospital. The average dilatation of all cases of primiparas at the time the first block was given was five and three-tenths centimeters, and the time necessary to attain complete dilatation was one hour and fifty-four minutes! As an average of all the group of the multiparas, the average dilatation at the time of the first block was four and six-tenths centimeters, and the time necessary to obtain complete dilatation, when averaged, was exactly the same as primiparas, one hour and fifty-four

minutes! From this, it can be seen that the blocks had an apparent effect of greatly increasing the rate of dilatation, and indeed, frequently one could feel the cervix dilating during the course of a rectal examination. This of course, does not mean that if sympathetic nerve blocks are started with the first pain of labor that all labors would be of only four hours' duration, as the progress of labor is usually more rapid as its termination is approached. However, there seems to be no question about the accelerating effect of these injections upon the progress of labor.

Of the forty-six primiparas, thirty-eight of the deliveries were spontaneous, two were by breech extraction, and six were by outlet forceps. In the multiparous group, the twenty-four deliveries were all spontaneous. All seventy of the babies were in excellent condition at birth, and in no instance was resuscitation necessary.

Blood loss was measured wherever possible. In many cases, due to a Duncan type of placental delivery or accidental addition, of amniotic fluid, or antiseptic solutions to the Pastore apparatus, blood loss had to be estimated, hence, the reason for the two figures. In primiparas, twenty-nine cases had a measured blood loss, the average being 245 cubic centimeters. Those estimated were seventeen in number, and the average estimated amount was 270 cubic centimeters. In the multiparous group, 208 cubic centimeters was the average estimated blood loss in fourteen cases, and 225 cubic centimeters was the average estimated blood loss in the other ten. It must be borne in mind, when examining these figures, that all of these cases had episiotomies of generous proportions, and that the blood loss from this incision is also included in these figures. There was one case of post-partum hemorrhage of 900 cubic centimeters, measured. This was in a primipara whose uterus became incarcerated in the pelvis. The bleeding stopped immediately after the uterus was lifted into the abdomen. There were no other cases of hemorrhage.

The average hospital stay for primiparas was 9.3 days post partum. There were three patients in this group who had a cervical obstruction to lochial drainage and a correspondingly morbid course. Temperature dropped immediately to normal upon establishing drainage by means of uterine aspiration. In the multiparous group, the average hospital stay was nine days post partum. There was one case of impaired

TABLE 11

	PRIMIPARA	MULTIPARA
LOA	14	8
ROA	7	7
LOT	7	1
ROT	6	4
LOP	5	2
ROP	5	2
LSP	1	0
RSA	1	0

lochia drainage with subsequent morbid course which was immediately relieved by uterine aspiration. There was one case of subinvolution in a para vi which was found at her six weeks' post-partum examination.

Almost all positions were encountered in this group of patients as can be seen by Table II.

Most of the babies were of normal size. A total of five out of the seventy were over 4,000 grams, and three were under 2,500 grams, the remainder being normal. Of the complications encountered, there were fourteen posterior presentations, two breeches, three premature babies, one toxemia, one cardiac case, one urinary tract infection, one patient who had had a previous cesarean section for bleeding, and one case had a blood tap on here second injection. The first ten in each of the two groups, primiparas and multiparas, received no medication other than the paravertebral sympathetic blocks and the perineal pudendal blocks for delivery. Thereafter, patients received on the average,  $\frac{2}{10}$  of a gram of sodium pentobarbital, providing delivery was not imminent. Nitrous oxide-oxygen mixture was given for the last one or two labor pains prior to delivery of the head, to ease the expulsive discomfort as well as the stretching of the labia.

### Discussion

This method produces no skin anesthetics, motor weakness or paresthesias. The patient can move about in bed to any position she desires, she can sleep or read as she wishes, and is able to maintain her food and fluid intake in a normal manner.

There seems to be no doubt that the first stage of labor is markedly accelerated by paravertebral nerve block. There is rapid dilatation of the cervix, apparently due to relaxation, as the quality and frequency of labor pains are completely unchanged.

In the case of the one toxemia in this series, blood pressure fell to normal, and the patient seemed clinically, as well as subjectively, improved. No conclusions can be drawn from this one case, but it at least gives promise of some benefit, and is not contraindicated.

It is not a panacea for all obstetrics and will not prevent any post-partum complications. One patient who had had four paravertebral blocks developed a post-partum thrombophlebitis, however, morbidity was decreased in this group although the number of cases is too small to draw extensive conclusions. Recovery is as rapid as in cases receiving other types of treatment. Complications numbered only one, and there is considerable question as to whether the method of analgesia was responsible or not. This was a patient who had an hysterical anesthesia to pain, but not to touch or to pressure, from a level at the clavicles down to the knees which was symmetrical, resolved slowly over a course of hours, and had no sequela. No hyperesthesias or paresthesias were found in any case.

All patients in this group were carefully observed and followed prenatally, through labor and delivery, during their post-partum course in the hospital, and at the six weeks' post-partum examination.

Multiparas were extremely enthusiastic, having had previous experience with childbirth without such relief. Primiparas were less enthusiastic because the blocks prevent the pain of uterine contractions only, and the perineal blocks prevent the pain of actual delivery, however there is no inhibition of the expulsive forces or the reflexes which are necessary for spontaneous delivery. These expulsive stimuli are those of pressure, and if these feelings are abolished, spontaneous delivery takes too long to accomplish, and often is impossible. Several patients have stated that it is not a pain so much as a discomfort comparable to the passage of "a large firm stool." The giving of nitrous oxide and oxygen for the last efforts of the second stage greatly relieves this discomfort.

All babies in this series were born in excellent condition, breathed and cried immediately and spontaneously, and were of good color. The course of the babies remained normal throughout the hospital stay.

To my knowledge, this is the first series of cases in which labor has been conducted by this method. Much more work must be done before definite conclusions can be reached. It may well be that ureteral catheters can be inserted through the lumbar puncture needles, and sealed in place with collodion and a continuous type of anesthesia be given. This will await further work.

### Summary

In all, seventy cases of labor were carefully observed and followed, and their pains were relieved by single or multiple paravertebral sympathetic blocks and perineal pudendal blocks. The method is safe and simple and without sequelae, and can be done without elaborate equipment or extensive technical training. It seems to definitely speed the dilatation of the cervix without the many tiny lacerations so frequently seen post partum. Spontaneous delivery is the rule. Contraindications to this procedure have been indicated. The first results from the management of labor by this method are gratifying, and further study is needed and is indicated.

### Conclusions

1. Pain stimuli from the uterus travel by way of the sympathetic system and enter the cord at the last of the thoracic rami communicantes.
2. The pain of labor can be relieved by blocking the sympathetic chains in the lumbar area of the back.
3. Blocking of these nerves apparently speeds the dilatation of the cervix.



4. A method for obtaining painless labor and childbirth and obtaining spontaneous delivery without difficulty has been presented.

The author wishes to take this opportunity to express his appreciation to Dr. H. Hathaway, Head of the Department of Anesthesia of the University of California Hospital, for helpful encouragement and advice; to Dr. John A. Kapstein for his untiring efforts and technical assistance in the gathering of the data without which this paper would have been impossible; and to Dr. Herbert F. Traut, Professor of Obstetrics and Gynecology at the University of California Medical School, for his invaluable criticism and suggestions in the preparation of this report.

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# INFORMATION REGARDING THE TIME OF HUMAN OVULATION DERIVED FROM A STUDY OF 3 UNFERTILIZED AND 11 FERTILIZED OVA\*

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IN AN effort to discover the time of human ovulation in the menstrual cycle, we utilize in this paper the data associated with 11† fertilized and 3 unfertilized human ova collected during our joint investigation. The 11 embryos were found in the extirpated uteri of surgical patients. One of the unfertilized eggs (St-39-2044) was isolated from a ripe follicle; the second and third (Pe-41-749; and Mu-43-19, respectively) were unfertilized ova washed out of tubes. We will first consider the unfertilized eggs and then the series of 11 young embryos.

## I. Unfertilized Ova

A. *A Follicular Egg in the Late Anaphase of the First Maturation Division.*—(St-39-2044), Dated Less than 1 Day Preovulatory.—

This ovum was obtained from its unruptured follicle after laparotomy on the eleventh day of the menstrual cycle. In this case, the onset of catamenia in 13 recorded cycles prior to operation had ranged from the twenty-fifth through the twenty-ninth days (*Mean*:  $27 \pm 2$  days).

A section of this egg, which was fixed within 1 hour after recovery (Fig. 1), shows the vitellus surrounded by granulosa cells and enclosing the eccentrically placed nucleus, represented by two blurred masses of chromosomes on opposite ends of a well-formed spindle. The apparent absence of a polar body and the position of the chromosomal masses indicate that this egg is in the late anaphase of the first maturation division. Fig. 2, a high-power view of the meiotic figure, shows the details of the spindle and the separating chromosomes.

## Estimation of the Time of Ovulation

To aid in computing the probable time of follicular rupture in the cases associated with the 3 unfertilized eggs, we have data derived from (1) endometrial histology; (2) histology of the follicle or the recent corpus luteum; and (3) cytology of the ovum itself (Table I). The

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One of these, because it is pathologic, could not be dated, and hence contributed no information as to ovulation time. Three others have not been included in this report, since they were found only recently and have not been adequately studied.

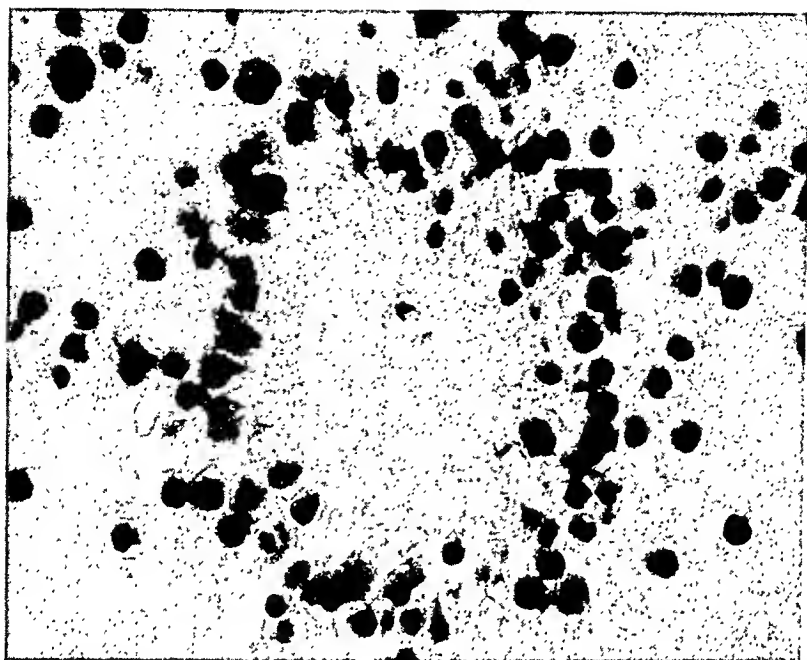


Fig. 1.—St-39-2044. A follicular egg in the late anaphase of the first maturation division (dated less than 1 day preovulatory). The ovum was fixed in Bouin's fluid, transferred to a plasma clot, and embedded in paraffin. Serial sections were cut at  $6\text{-}2/3\mu$ , and stained with hematoxylin and eosin.  $\times 450$ .

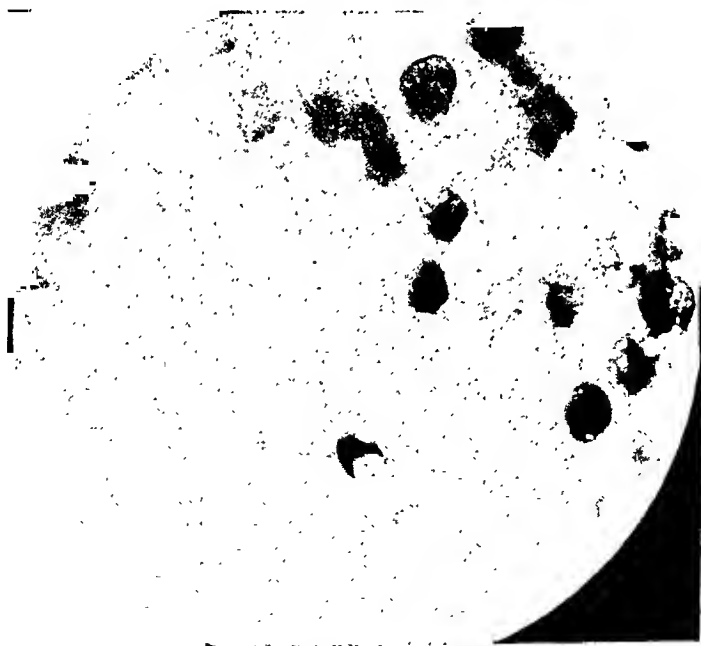


Fig. 2.—St-39-2044. High-power view of the meiotic figure. The small gray arc, representing the opposite mass of chromosomes, appeared more clearly defined in the next serial section.  $\times 1000$ .

catamenial history of the patient is of value for comparing the estimated length of the cycle under consideration in each particular case with the actual lengths of previous cycles.



Fig. 3.—St-39-2044. Endometrium in active late proliferation. Fixed in alcohol-formalin; embedded in celloidin; sections cut at about  $15\mu$ , and stained with hematoxylin and eosin.  $\times 200$ .

(1) *Endometrial Histology*.—On the eleventh day of the cycle, the endometrium in the case associated with the ripe follicular egg was still in very active late proliferation (Fig. 3). In accordance with our current standards, based on a theoretical cycle of 27 days, with cata-

TABLE I. TIME OF OVULATION COMPUTED FROM DATA OF 3 UNFERTILIZED OVA

CASE	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ENDO-ME-TRIAL DATING	NEXT EXPECTED PERIOD (NEP) BASED ON ENDOME-TRIAL DATING	AGE OF FOLLICLE OR CORPUS LUTEUM	ES-TIMATED AGE OF OVUM ON DAY OF OPERA-TION (DAYS)	ESTI-MATED DAY OF OVULA-TION	INTERVAL BETWEEN ESTI-MATED DAY OF OVULATION AND NEP (DAYS)	NEXT EXPECTED PERIOD (NEP) BASED ON CTA. HISTORY
St-39-2044	11	<14*	>25	Cells of theca interna show transition from connective tissue to lutein type	0 to 1† (Preovu-latory)	11 to 12	>14 to >13	27 $\pm$ 2 (13)*‡
Pe-41-749	14	16	26	2 to 3 days	2 to 3	11 to 12	15 to 14	28 $\pm$ 2 (7)*
Mu-43-19	13	17	24	3 to 4 days	3 to 4	9 to 10	15 to 14	28 (1)

\*Late proliferative phase.

†Ovulation would probably have occurred from a few hours to 1 day later.

‡Parentheses enclose number of cycles studied; \* indicates menstrual dates were from a written record.

menia on the twenty-eighth day,<sup>1, 2</sup> we have dated it as somewhat less than 14 days. From the endometrial dating we may estimate when the next menstruation is due: in this case, in somewhat more than 14 days ( $28 - <14 = >14$ ). Since operation took place on the eleventh day of the cycle, the next expected period would be due somewhat later than the twenty-fifth day:  $11 + >14 = >25$  (Table I, Column 4). This estimate of the next anticipated period is in accordance with the previous catamenial history of the patient, as recorded in the last column of Table I.



Fig. 4.—St-39-2044. Wall of follicle from which the egg was recovered, showing transition of theca interna and granulosa layer toward luteinization. Fixed in formalin; embedded in celloidin; sections cut at about  $15\mu$ , and stained with hematoxylin and eosin.  $\times 100$ .

(2) *Histology of the Follicle.*—Although the follicle was slightly mutilated, its structure was still sufficiently well preserved to show that the connective tissue cells of the theca interna were already well advanced toward complete luteinization and the granulosa cells likewise were changing in that direction (Fig. 4). The establishment of a true corpus luteum was imminent.

(3) *Cytology of the Egg.*—Since the ovum was in the process of completing the first maturation division which would have resulted in the formation of the first polar body, it was obviously on the verge of ovula-

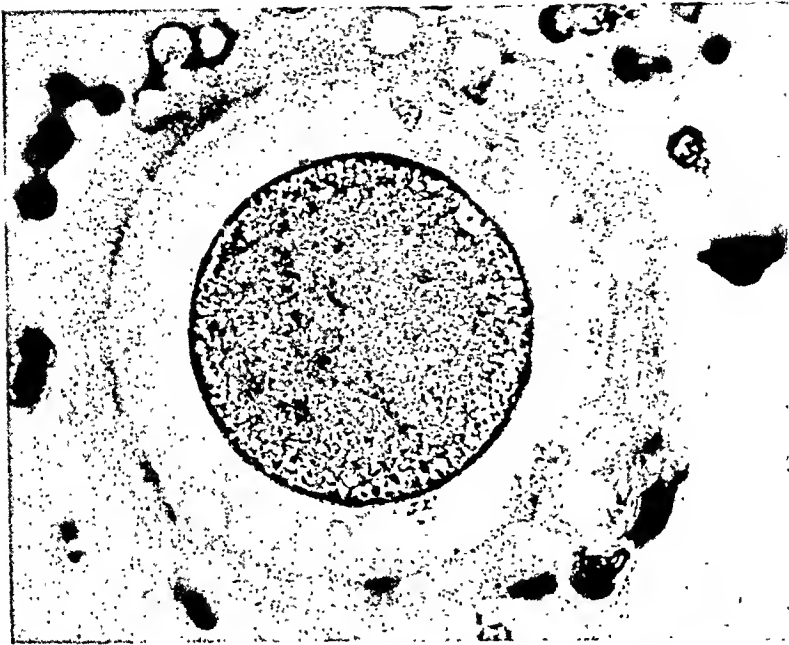


Fig. 5.—Pe-41-749. A tubal egg (dated 2 to 3 days postovulatory). The ovum was photographed before fixation in a hanging-drop of saline solution about 36 hours after it had been washed out of the tube.  $\times 450$ .

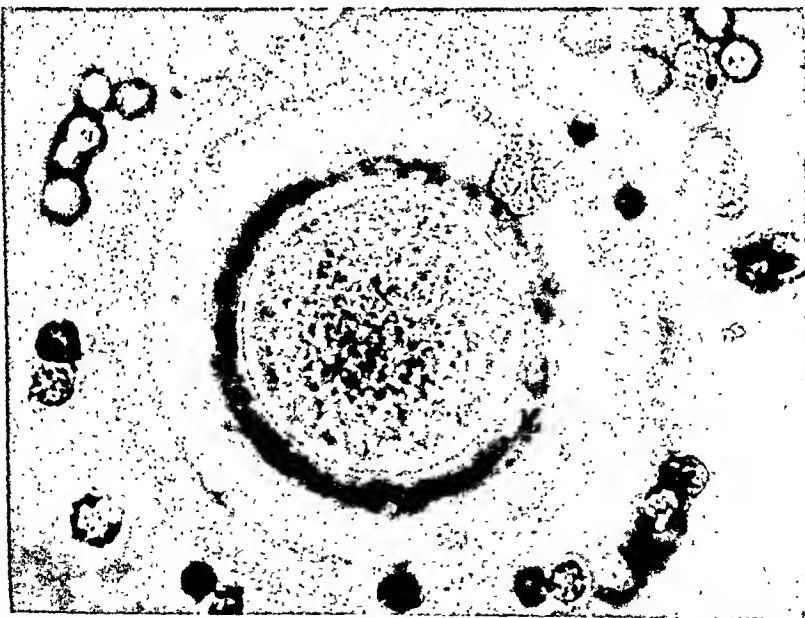


Fig. 6.—Pe-41-749. Same as Fig. 5, but photographed in a paramedian optical plane. Note object suggestive of polar body outside the vitellus.  $\times 450$ .

tion. This stage in the rabbit would be followed by ovulation about 2 to 4 hours later.<sup>3</sup> Because no corresponding data in the human being are available, we may estimate that ovulation would doubtless have occurred within not more than 1 day; therefore we dated this egg as 0 to 1 day preovulatory (Table I, Col. 6).

*Computation of the Length of the Postovulatory Phase.*—Since the egg had been recovered on the eleventh day of the cycle, we may consider that had operation not taken place, ovulation would have occurred between the eleventh and twelfth days of the cycle (Table I, Col. 7). Subtracting this value (11-12) from the day of onset of the next estimated period, >25 (Col. 4), we obtain:

Next Expected Period (NEP) Based on Endometrial Dating	>25	>25 (Col. 4)
Estimated Day of Ovulation	11 to 12	(Col. 7)
Interval Between Estimated Day of Ovulation and NEP (Days)	>14 to >13	(Col. 8)

In other words, the postovulatory phase is here estimated to be somewhat more than 14 to 13 days long.

#### B. A Tubal Egg (Pe-41-749), Dated 2 to 3 Days Postovulatory.—

The second unfertilized egg was washed out of the tube on the fourteenth day of the menstrual cycle. Recorded dates of catamenial onset for 7 cycles preceding operation had ranged between day 26 and day 30 (*Mean*:  $28 \pm 2$  days).

The egg was photographed about 36 hours after it had been washed out of the tube (Figs. 5 and 6). During this interval, it had been kept for about 6 hours at room temperature in tubal washings with Loeke's solution; 17 hours at incubation temperature in the patient's serum; 8 hours at room temperature, part of the time in the patient's serum, and part in a mixture of serum and saline solution; and 5 hours in the icebox in a hanging-drop of saline solution. Undoubtedly, some infection of the culture medium had occurred during incubation. In spite of this, however, the egg appears to be fairly well preserved with no obvious evidence of degeneration, unless the coarsely granular and finely vacuolated cytoplasm indicates beginning atresia. The granulosa cells and the zona pellucida are clearly recorded in the photographs. In Fig. 6, taken in a paramedian optical plane, an object suggestive of a polar body is lying outside the vitellus, but the boundaries of the perivitelline space are not definable.

### Estimation of the Time of Ovulation

(1) *Endometrial Histology.*—On the fourteenth day of the cycle the endometrium showed definite evidence of a progestational change, as manifested by the vacuolization of the infranuclear cytoplasm of the glandular epithelium (Fig. 7). There was as yet, however, no lining-up of the nuclei; in other words, they were still in that position which we call "pseudostratification." The glands were characteristically twisted and ribboned. This stage we designate as of the sixteenth day;

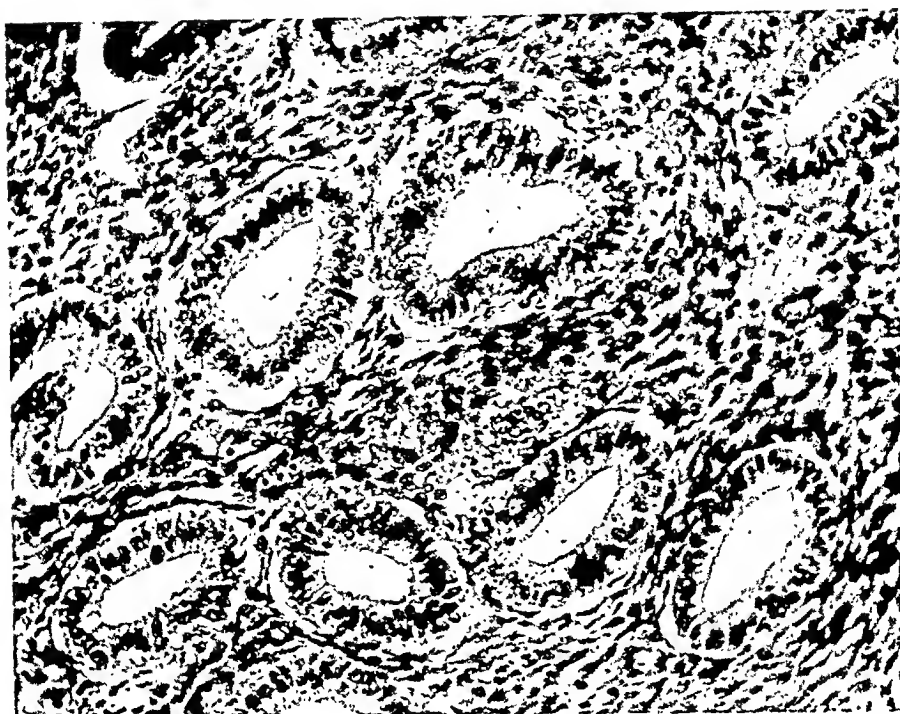


Fig. 7.—Pe-41-749. Endometrium characteristic of the 16th day of a 27-day cycle. Fixed in Boulin's fluid; embedded in paraffin; sections cut at  $6\text{--}1\frac{1}{4}\mu$ ; stained with hematoxylin and eosin.  $\times 200$ .

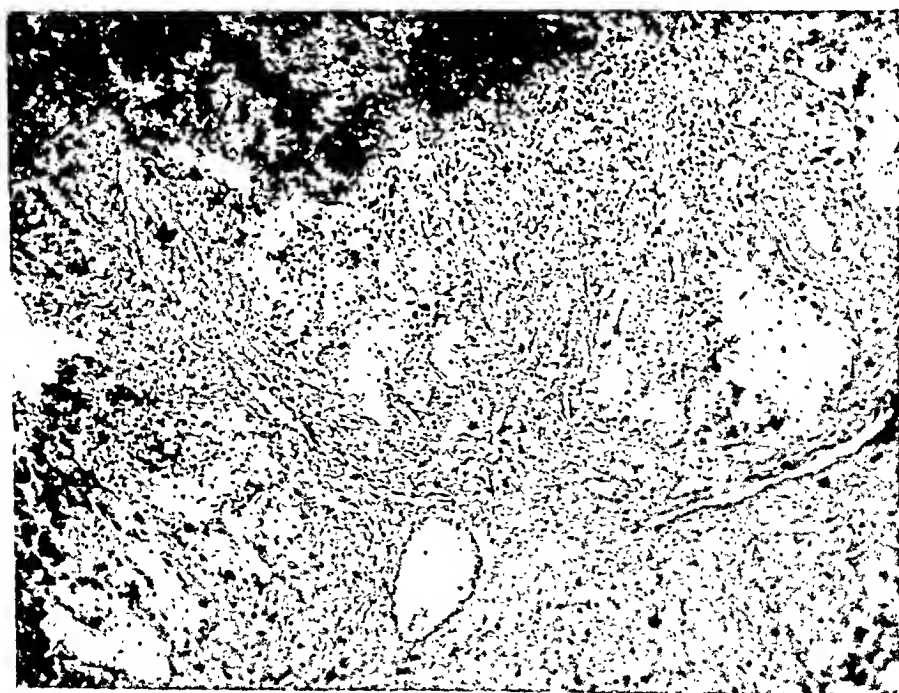


Fig. 8.—Pe-41-749. Corpus luteum, somewhat traumatized, dated as 2 to 3 days. Fixed in Zenker's solution; embedded in paraffin; sections cut at  $6\text{--}2\frac{2}{3}\mu$ , and stained with hematoxylin and eosin.  $\times 100$ .



that is, if menstruation is considered to take place on the twenty-eighth day of a standard cycle, this is to be regarded as a "minus 12-day" endometrium, dating backward from the onset of the next catamenia. Twelve days would be expected to elapse before the beginning of the next flow. Since operation had taken place on the fourteenth day of the cycle, the next period would then be due on the twenty-sixth day (Col. 4). As in the first case cited, the estimated length of the particular cycle under consideration agrees with the catamenial history (Last Column).

(2) *Histology of the Corpus Luteum*.—On section the corpus luteum corresponding to the tube from which the ovum had been recovered showed large areas of extravasated blood among the granulosa cells; some of these blood-filled spaces, especially near the central cavity, had undergone slight endothelialization (Fig. 8). A few fibroblasts were also noted near the central border of the granulosa cell layer. On the basis of this histologic picture, and in accordance with Brewer's dating of corpora lutea,<sup>4</sup> we judged this gland to be between 2 and 3 days old.

(3) *Cytology of the Ovum*.—Due probably to the long interval between recovery of the egg and fixation (more than 38 hours), very little could be deduced from the stained section. Even that object which in the fresh specimen suggested a polar body could not be identified as such in the microscopic preparation. A large, round, well-defined nucleus, sparsely supplied with discrete particles of chromatin material, lay slightly off center within a highly vacuolated cell body.\* The estimation of the time of ovulation in this particular case, therefore, was derived mainly from a consideration of the histology of the endometrium and of the corpus luteum.

*Computation of the Length of the Postovulatory Phase*.—In view of the estimated age of the corpus luteum (3 to 2 days) and of the endometrium (16 days), ovulation was judged to have taken place between 3 and 2 days prior to operation; i.e., between the eleventh and twelfth days of the cycle:  $14 - (3 \text{ to } 2) = 11 \text{ to } 12$  (Col. 7). Subtracting this value (11-12) from the day of onset of the next estimated period, 26 (Col. 4), we obtain:

Next Expected Period (NEP) Based on Endometrial Dating	26	26 (Col. 4)
Estimated Day of Ovulation	11 to 12	(Col. 7)

Interval Between Estimated Day of Ovulation and NEP (Days) 15 to 14 (Col. 8)

The estimated postovulatory phase is therefore between 15 and 14 days in length. In the first case it was somewhat more than 14 to 13 days long.

#### C. A Tubal Egg (Mu-43-19), Dated 3 to 4 Days Postovulatory.—

The third unfertilized ovum was found in tubal washings after laparotomy on the thirteenth day of the cycle. No written record of menstruation was available. The patient stated that her last period had begun on the twenty-eighth day of the cycle.

This egg, not as well preserved as the second one, showed signs of beginning degeneration. The apparent presence of one, or possibly

\*The vesicular form of the nucleus may be due to a refusion of nuclear elements, as has been observed in rabbit ova following culture or activation by various agents (including low temperature), or by a combination of activating agents and culture.<sup>1, 2, 6</sup>

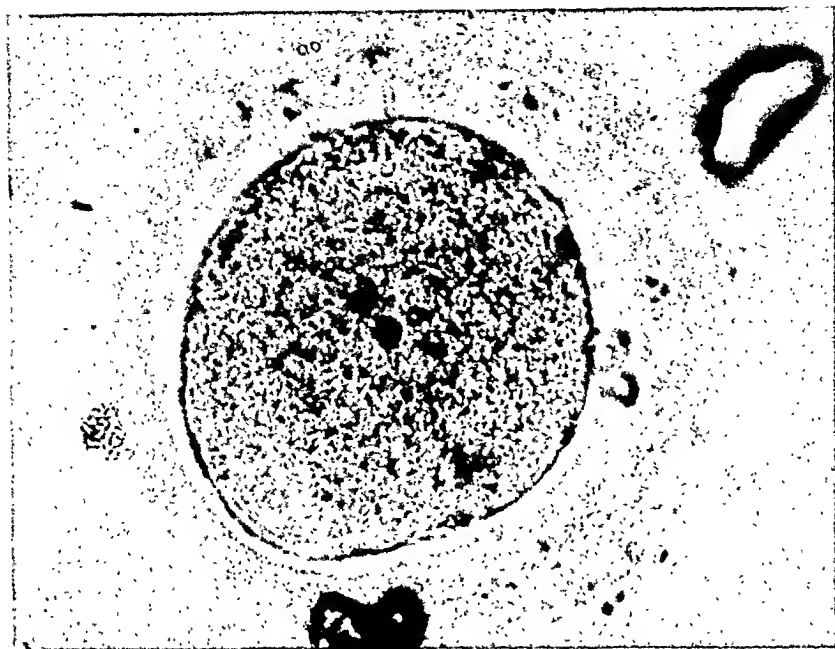


Fig. 9.—Mu-43-19. A tubal egg (dated 3 to 4 days postovulatory). The ovum was photographed before fixation in a hanging-drop of Locke's solution about 9 hours after it had been washed out of the tube.  $\times 425$ .

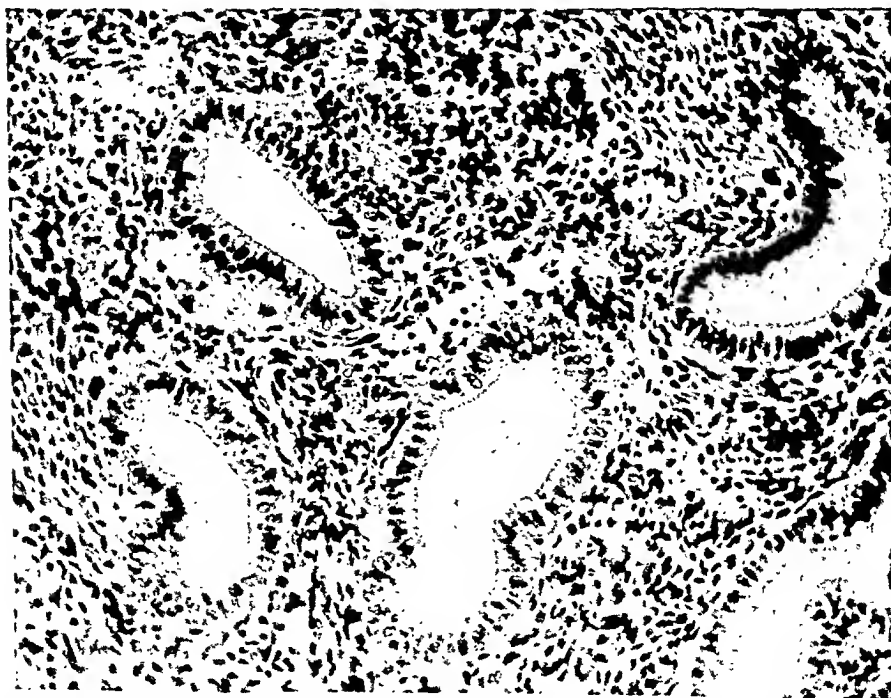


Fig. 10.—Mu-43-19. Endometrium characteristic of the 17th day of a 27-day cycle. Fixed in Bouin's fluid; embedded in paraffin; sections cut at  $6\frac{1}{4}\mu$ ; stained with hematoxylin and eosin.  $\times 200$ .

two, polar bodies suggested that at least the first maturation division had been completed (Fig. 9).

This specimen was photographed about 9 hours after it had been washed out of the tube. During this interval the egg had been kept in Loeke's solution at room temperature—for about 7 hours in a dish, and for the remaining 2 hours in a hanging-drop.

### Estimation of the Time of Ovulation

(1) *Endometrial Histology*.—As is seen in Fig. 10, the endometrium had advanced further toward the development of a true secretory phase than in the second case (Fig. 7). In contrast to their condition in the latter, the nuclei here were no longer in the position of pseudostratification, although infranuclear vacuolization was still marked in many glands, and mitotic figures, while present, were scarce. The specimen was accordingly rated as of day 17; that is, 11 days would be expected to ensue before the onset of the next catamenia. Since operation had taken place on the thirteenth day of the cycle, the next period would be due on the twenty-fourth day of the cycle (Col. 4).

(2) *Histology of the Corpus Luteum*.—The endothelialization of the blood spaces among the granulosa cells, and the fibroblastic activity in the central cavity (Fig. 11), were more advanced here than in the second case (Fig. 8), although vascularization was still imperfect and no binding connective tissue was apparent. Some extravasated blood, a prominent feature of the second case, was present here to a less degree. On the basis of this histologic picture, the corpus luteum was judged to be slightly older than that of the second case; i.e., it was dated as 3 to 4 days postovulatory.

*Computation of the Length of the Postovulatory Phase*.—This egg has not as yet been sectioned. Since, from its appearance in the fresh state, little could be deduced besides the possible presence of one or two polar bodies, here again, the estimation of the time of ovulation is based mainly on the histology of the endometrium and of the corpus luteum. In view of the estimated age of the corpus luteum (4 to 3 days) and of the endometrium (17 days), ovulation was judged to have taken place between 4 and 3 days prior to operation; i.e., between the ninth and tenth days of the cycle:  $13 - (4 \text{ to } 3) = 9 \text{ to } 10$  (Col. 7). Subtracting this value (9-10) from the day of onset of the next estimated period, 24 (Col. 4), we obtain:

Next Estimated Period (NEP) Based on Endometrial Dating	24	24 (Col. 4)
Estimated Day of Ovulation	9 to 10	(Col. 7)

Interval Between Estimated Day of Ovulation and NEP (Days) 15 to 14 (Col. 8)

In this case, therefore, the postovulatory phase is 15 to 14 days long. This value is the same as was obtained in the second case, although the estimated lengths of the cycles under consideration in the two cases varied by 2 days; i.e., the next expected period in Pe-41-749 was due on the twenty-sixth day of the cycle, whereas that in Mn-43-19 was due on the twenty-fourth day of the cycle. The lengths of the preovulatory phases (11 to 12 days in Pe-41-749, and 9 to 10 days in Mu-43-19) varied by 1 to 3 days, while the corresponding postovulatory phases were constant.

## II. Fertilized Ova

In a recent communication<sup>7</sup> we have described how data derived from a study of 11 young human embryos may be utilized for estimating ovulation time. In the present report we will briefly explain our procedure in this connection, and consider how conclusions so reached compare with those obtained from the 3 unfertilized eggs discussed previously.



Fig. 11.—Mu-43-19. Corpus luteum dated as 3 to 4 days. Fixed in Bouin's fluid; embedded in paraffin; sections cut at  $6\text{--}1\frac{1}{4}\mu$ , and stained with hematoxylin and eosin.  $\times 100$ .

### Estimation of the Time of Ovulation

As seen in Table II, in order to compute the time of ovulation from the available embryologic material, one must have information as to the following: (1) age of embryo; and (2) endometrial histology.

(1) *Age of Embryo*.—The ages of 11 human embryos, listed in Table II (Col. 2), have been estimated by Doctors Streeter and Heuser of the Department of Embryology of the Carnegie Institution of Washington, by comparing the development of these specimens with that of monkey conceptuses of known ovulation ages. The ages are recorded as mean values; for example, in the first case, Mu-8020, the figure 7.5 indicates that this particular ovum is judged to be between 7 and 8 days old.

(2) *Endometrial Histology*.—Column 3 lists for each of the 11 cases the estimated number of days (after the day of operation) that, in view of its histology, would be required for the endometrium to reach the 28-day, or catamenial, stage. Thus, in Mu-8020, we considered, on the basis of our endometrial standards, that secretory changes had gone on to about the 22-day stage; hence 6 days would be expected to elapse before the onset of flow.

TABLE II. TIME OF OVULATION COMPUTED FROM DATA OF 11 FERTILIZED OVA

CASE	MEAN ESTIMATED AGE OF OVUM (DAYS)	ESTIMATED INTERVAL BE- TWEEN OPERATION AND NEXT CATA- MENIA AS JUDGED BY CONDITION OF ENDOMETRIUM (DAYS)	INTERVAL BETWEEN ESTIMATED OVULATION AND ANTICIPATED MENSTRU- ATION (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ESTIMATED PRE- OVULATORY INTERVAL (DAYS)
Mu- 8020*	7.5	6	13.5	24	16.5
Wi- 8004	9.5	2	11.5	25	15.5
Si- 7699	11.5	3	14.5	25	13.5
Tr- 7770	11.5†	3	14.5†	31	19.5†
Er- 7850	11.5†	3	14.5†	31	19.5†
Sm- 8000	11.5†	3	14.5†	28	16.5†
Re- 7950	12.0	5	17.0	26	14.0
Al- 7700	12.5	2	14.5	29	16.5
Br- 7800	13.0†	2	15.0†	32	19.0†
Ru- 7801	13.5	2	15.5	28	14.5
Bu- 7802	16.5	0	16.5	33	16.5

\*Refers to the accession number of the Carnegie Institution of Washington.

†Indicates abnormal specimen the age of which could not be estimated as accurately as in the cases of normal ova.

*Computation of the Length of the Postovulatory Phase.*—The length of the postovulatory phase, or the interval between the estimated time of ovulation and anticipated menstruation (Col. 4), is obtained by adding the corresponding figures in columns 2 and 3. In 8 out of the 11 cases listed, the values for the postovulatory phase fall within the limits of 16 to 12 ( $14 \pm 2$ ) days. In 2 of the exceptions, Wi-8004 and Bu-7802, the variation from the outermost limits is 0.5 day, and in the third exception, Re-7950, the deviation is 1 day.

*Computation of the Length of the Preovulatory Phase.*—This is obtained by subtracting in each case the mean estimated age of the ovum (Col. 2) from the day of the cycle on which operation took place (Col. 5). The resulting values for the lengths of the preovulatory phase in the 11 cases listed (Col. 6) show a definitely greater variation than do those for the postovulatory phase (Col. 4).

*Computation of the Length of the Estimated Postovulatory Phase in Terms of Percentiles of the Menstrual Cycle.*—To discover the temporal position of ovulation with respect to the next anticipated period in cycles of different lengths, we also followed Reynolds's suggestion and divided each estimated cycle into percentiles; the estimated time of ovulation was then expressed as occurring in a certain percentile of the cycle with reference to the next expected catamenia (Table III, Col. 3).

In order to determine to what extent the estimated postovulatory phase varies in length from the theoretical phase (14 days), this latter was calculated in percentiles for each case (Col. 4). It should be noted that the computations by which the figures in column 3 were obtained involve the use of 2 imponderables: (1) the age of the embryo; and (2) the dating of the endometrium. In column 4, on the other hand, only 1 uncertain value enters into the calculations; i.e., the dating of the endometrium. If columns 3 and 4 are compared, it will be seen that, with a few exceptions, they are in fair agreement. The degree of correlation expresses the accuracy of the statement that ovulation occurs 14 days before menstruation. Even where the deviation from the theoretical value

seems to be most striking, +9.6 per cent (Re-7950), the difference is really not as great as it appears to be, for this figure represents not quite 0.1 of a cycle, and in a 30-day cycle,\* the divergence between the estimated and theoretical value is only 3 days, which falls just 1 day outside the theoretical deviation from the mean,  $\pm 2$  days.

The close degree of correlation between the values in columns 3 and 4 indicates very strongly that ovulation takes place about 14 days before the onset of the next period. The data obtained from the 3 unfertilized eggs, discussed above, point to the same conclusion.

TABLE III. TIME OF OVULATION COMPUTED FROM DATA OF 11 FERTILIZED OVA EXPRESSED IN PERCENTILES OF MENSTRUAL CYCLE PRECEDING NEXT EXPECTED PERIOD (NEP)

CASE	NEXT EXPECTED PERIOD (NEP) BASED ON ENDOMETRIAL DATING*	% MENSTRUAL CYCLE AT COMPUTED TIME OF OVULATION†	% MENSTRUAL CYCLE 14 DAYS BEFORE COMPUTED NEP**	NEXT EXPECTED PERIOD (NEP) BASED ON CTA. HISTORY‡
Mu- 8020*	30	45.0	46.7	30 $\pm$ 2 (2)*
Wi- 8004	27	42.6	51.9	34 (1)*
Si- 7699	28	51.8	50.0	27.5 $\pm$ 1.5 (6)*
Tr- 7770	34	42.6†	41.2	32 $\pm$ 1 (2)*
Er- 7850	34	42.6†	41.2	33 $\pm$ 1 (2)
Sm- 8000	31	46.8†	45.2	32 $\pm$ 0 (2)*
Re- 7950	31	54.8	45.2	30 $\pm$ 3 (7)*
Al- 7700	31	46.8	45.2	34.5 $\pm$ 1.5 (4)
Br- 7800	34	44.1†	41.2	28 $\pm$ 3 (3)*
Ru- 7801	30	51.7	46.7	26 $\pm$ 2 (4)*
Bu- 7802	33	50.0	42.4	29.5 $\pm$ 3.5 (2)
Average	31.2	47.2	45.2	
Range	27-34	42.6-54.8	41.2-51.9	
Mean	30.5	48.7	46.6	
Deviation	$\pm 3.5$	$\pm 6.1$	$\pm 5.4$	

\*Refers to the accession number of the Carnegie Institution of Washington.

\*These values were obtained by adding the figures of Column 3 in Table II [Estimated Interval Between Operation and Next Catamenia as Judged by Condition of Endometrium] to the corresponding figures of column 5 in the same table (Day of Cycle on Which Operation Took Place).

†These values were obtained by dividing the figures of Column 4 in Table II (Interval Between Estimated Ovulation And Anticipated Menstruation) by the corresponding figures of Column 2 in Table III [Next Expected Period (NEP) Based On Endometrial Dating], and multiplying the quotient by 100.

‡These values were obtained by dividing 14 by the figures of Column 2 in Table III [Next Expected Period (NEP) Based On Endometrial Dating], and multiplying the quotient by 100.

\*\*Indicates abnormal specimen the age of which could not be estimated as accurately as in the cases of normal ova.

§Parentheses enclose number of cycles studied; \* indicates menstrual dates were from a written record.

## Summary and Conclusions

1. Data relating to 14 human ova (3 unfertilized and 11 fertilized) have been considered with a view to discover the time of ovulation.

2. In the cases associated with 3 unfertilized eggs, the lengths of the preovulatory and postovulatory phases have been calculated, utilizing the histology of the endometrium and of the ripe follicle or early corpus luteum, in conjunction with the menstrual history, and to some extent the cytology of the ovum itself. By means of these data, it was found,

\*Since the next expected period of Re-7950 was due on the thirty-first day, the cycle should have been 30 days long.

in the 2 cases of tubal eggs, that while the preovulatory phases varied by 1 to 3 days (ninth to tenth, and eleventh to twelfth days of the cycle, respectively), the corresponding computed postovulatory phases were identical: 15 to 14 days. In the case of a ripe follicular egg, ovulation was estimated as due between the eleventh and twelfth days of the cycle; the postovulatory phase would then have been somewhat more than 14 to 13 days long.

3. In 11 cases of fertilized ova, the lengths of the pre- and post-ovulatory phases were likewise calculated; here, in addition to the histology of the endometrium, and the related catamenial data, the mean estimated age of the embryo was utilized. In 8 of the 11 cases (72.7 per cent), the estimated postovulatory phase fell within the limits of 16 to 12 ( $14 \pm 2$ ) days. In 2 of the 3 exceptions, the variation from the outermost limits of the theoretical range was 0.5 day, while in the third exception, the deviation was 1 day.

When ovulation in these 11 cases was expressed as occurring in a certain percentile of the respective menstrual cycle with reference to the next expected period, the average postovulatory phase was found to occupy 47.2 per cent of the cycle. Upon substituting for the experimentally derived estimated length of the postovulatory phase, the theoretical figure, 14, in each case, the average value for these 14 post-ovulatory days was 45.2 per cent of the cycle. The correlation of these two values, 47.2 per cent and 45.2 per cent, expresses the proximity of probable ovulation time in these cases to the fourteenth day before menstruation. These averages differ by only 2 per cent of the cycle length, which in our 11 cases averaged 30.2 days. This difference is only 0.6 day, which is much less than the commonly accepted deviation of  $\pm 2$  days from the theoretical mean length of the postovulatory phase, 14 days.

4. Data from 3 unfertilized ova, as well as from a series of 11 fertilized ova, indicate that ovulation takes place about 14 days before the first day of the next expected period.

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# CALCIUM, PHOSPHORUS, IRON AND NITROGEN BALANCES IN PREGNANT WOMEN\*†

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MANY articles have been published about the calcium, phosphorus, iron, nitrogen and vitamin D requirements during pregnancy. They contain various statements as to the efficacy of these substances in preventing many of the complications of pregnancy and ensuring the normal development of the fetus. However, there is considerable divergence of opinion because the reports have been based largely on the patient's comments regarding improvement in the various symptoms. The clinical evaluation of substances or methods is always open to question if based on the patient's symptoms. The appraisal should be based on the accumulation of a large amount of pertinent data from an adequate number of patients. The purpose of our study was to note the influence of added calcium, phosphorus, iron and vitamins A and D upon the clinical course of the pregnancy, puerperium, and baby as well as the effect upon the blood hemoglobin, calcium, phosphorus, and serum protein.

The total number of patients studied was 553. These were divided into four groups:

I. Control.

II. These patients receive a proprietary cereal for its calcium, phosphorus and iron content.

III. The patients in this group were given 39,900 international units of vitamin A, and 5,550 international units of vitamin D daily.

IV. The cereal and the previously described amounts of vitamins A and D were administered to the patients in this group.

The groups were selected at random and yet they showed rather striking homogeneity as can be seen from the following table:

	NO.	AV. AGE.	GRAVIDA
I	175	25.5	2.1
II	179	25.5	2.2
III	98	25.3	2.0
IV	102	24.4	1.7

\*This title is incorrect but it is used in order that the article to which it belongs and which was published in this *Journal* in 1943 is listed in the Index Medicus.

The correct title for this report is "The Effect of Complementing the Diet in Pregnancy with Calcium, Phosphorus, Iron and Vitamins A and D."

†This study was supported in part by a grant from Mead, Johnson and Company, who supplied the special cereal and vitamins.



Patients in Groups II, III, and IV received the same medication throughout pregnancy. Each patient was instructed to ingest 100 Gm. of the proprietary cereal daily, which would have assured an additional intake of 0.78 Gm. of calcium, 0.62 Gm. of phosphorus and 30 mg. of iron, but the average amount of the cereal taken daily ranged from 30 to 50 Gm. The patients were given a supply of cereal and vitamins sufficient for the entire family, with the thought that this might encourage the patients to take their shares daily.

All the patients studied were in the low income group. That their diets were fairly comparable can be seen from the consumption of milk by the various groups listed in the table below.

	I	II	III	IV	TOTAL
Milk					
½ pt. or less	41%	31%	21%	20%	25%
1 to 1½ pts.	44%	43%	42%	42%	47%
1 qt. or more	15%	26%	37%	39%	28%

Factors resulting in the low milk consumption were economic, dislike for milk, belief that milk was not well tolerated, that it was constipating, and lack of appetite.

Foods eaten at least once daily were:

Meat	71 per cent of the patients
Butter	85 per cent of the patients
Fresh fruits	82 per cent of the patients

Vegetables were used daily by 91 per cent of the group, and the majority used them more often. Only 30 per cent used eggs daily, although 57 per cent used eggs at least four times per week. The impression is that the group of patients consuming from one to three eggs or less per week includes a high percentage of those failing to include whole-grain cereal and bread, and using little cheese in the diet.

The majority of those patients using one quart or more of milk selected a sufficient variety of foods to insure a fair diet. The same is true of the groups using one and one and one-half pints of milk, the limiting factor in these groups being the restricted milk intake.

Where milk or the total food intake was low, an effort was made to encourage the patient to increase the intake; otherwise little attempt was made to change the dietary habits.

The nutritionist's data are of interest in view of the following observations: Two to five patients from each group (total 14) were periodically admitted to the hospital for balance studies. Twenty-four studies were made before delivery. The phosphorus balances were all positive. There was one negative balance for calcium, one for iron and two for nitrogen. Since the experiments began on the second hospital day, the patients must have been eating an adequate diet with regard to the substances studied before admission.

The blood chemistry results are striking in their uniformity. From a glance at the accompanying table some changes in the constituents listed can be noted, but when the results are treated statistically these changes are not found to be significant.

Table I lists the serum calcium concentration during pregnancy and the puerperium. The data in the control group agree with most other recorded calcium concentrations during pregnancy. Our data indicate a change from 10.2 to 9.9, a difference which when treated statistically is not significant. Our figure of 9.9 mg. per cent in the third trimester of normal pregnancy agrees well with that of 9.5 at term given by Bodansky.<sup>1</sup> There is a rise in calcium concentration post partum but this rise is not significant statistically. Groups II, III, and IV had a slightly higher calcium concentration during pregnancy than the control group but again these differences are too small to be significant. Among the three test groups the calcium concentrations are almost identical.

In view of the work of Mull and Bill<sup>5</sup> in which they claimed that the calcium in pregnancy is decreased from 9.86 to 9.64 during the first four months of the year and 10.46 to 9.90 the remainder of the year, we arranged our data with respect to the month of the year and found that seasonal variations were not significant. Patients were also arranged with regard to weeks of gestation but no significant variations were found.

Attempts have been made to increase the normal serum calcium by the ingestion of calcium salts and vitamin D, or the injection of parathormone. The ingestion of adequate amounts of calcium will increase the serum calcium from 1 to 3 mg. per cent. The administration of vitamin D and parathormone will also cause an increase in the serum calcium up to 100 per cent, but the hypercalcemia cannot be maintained, and such high levels are dangerous to life. A normal concentration of serum calcium is best ensured by an intake of foods containing an adequate amount of calcium, phosphorus and vitamin D.

Chemical studies have demonstrated that calcium is present in several forms; namely; nondiffusible, which is bound to the serum protein, and diffusible, which can be divided into an ionized and a nonionized form. We have calculated the amount of diffusible serum calcium for the various groups and the various periods of pregnancy, according to McLean and Hastings<sup>4</sup> graph. The averages ranged from 4.4 to 5.1 mg. per cent, which are normal figures. There is no significant difference between groups or periods of pregnancy.

Phosphorus is just as important a constituent of bone and teeth as calcium and yet most attention has been directed to calcium. The amount of phosphorus in food is, in general, greater than calcium and the intake is more likely to be adequate. Perhaps that explains why the results on phosphorus (Table II) in our series of pregnancy patients are

TABLE I. SERUM CALCIUM—Mg. PER CENT

	1ST TRIMESTER		2ND TRIMESTER		3RD TRIMESTER		2 WKS. POST PARTUM		6 WKS. POST PARTUM	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Group I	10.2	0.086	9.9	0.223	9.9	0.128	10.3	0.192	11.2	0.158
Group II			10.2	0.260	10.4	0.171	10.7	0.172	11.3	0.209
Group III			10.1	0.215	10.6	0.189	10.2	0.236	10.8	0.229
Group IV			10.4	0.151	10.3	0.102	10.5	0.154	10.8	0.140

S.E. = Standard Error.

TABLE II. SERUM PHOSPHORUS—Mg. PER CENT

	1ST TRIMESTER		2ND TRIMESTER		3RD TRIMESTER		2 WKS. POST PARTUM		6 WKS. POST PARTUM	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Group I	4.0	0.069	4.2	0.101	3.4	0.126	4.5	0.091	4.3	0.117
Group II			3.9	0.154	3.8	0.142	4.3	0.120	4.1	0.137
Group III			4.2	0.150	4.2	0.221	4.3	0.108	4.1	0.104
Group IV			3.9	0.131	4.2	0.113	4.2	0.077	4.1	0.105

S.E. = Standard Error.

TABLE III. HEMOGLOBIN—GM. PER CENT

	1ST TRIMESTER		2ND TRIMESTER		3RD TRIMESTER		2 WKS. POST PARTUM		6 WKS. POST PARTUM	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Group I	12.2	0.066	11.8	0.093	12.0	0.130	12.0	0.150	12.7	0.175
Group II			11.5	0.095	11.5	0.102	12.3	0.154	12.7	0.128
Group III			11.5	0.108	11.7	0.139	12.2	0.202	12.8	0.151
Group IV			11.7	0.099	11.7	0.130	12.4	0.189	13.0	0.140
HEMATOCRIT PER CENT										
Group I	38.2	0.151	36.1	0.236	36.2	0.293	37.0	0.433	40.1	0.538
Group II			35.4	0.224	35.5	0.167	37.1	0.551	39.8	0.338
Group III			35.9	0.298	35.6	0.441	37.5	0.556	39.2	0.426
Group IV			36.5	0.262	36.0	0.314	37.0	0.581	40.0	0.488

S.E. = Standard Error.

TABLE IV. SERUM PROTEIN—GM. PER CENT

	1ST TRIMESTER		2ND TRIMESTER		3RD TRIMESTER		2 WKS. POST PARTUM		6 WKS. POST PARTUM	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Group I	6.84	0.038	6.6	0.358	6.8	0.067	6.7	0.087	7.3	0.083
Group II			6.8	0.057	6.7	0.062	6.6	0.129	7.2	0.094
Group III			6.8	0.062	6.8	0.079	6.8	0.088	7.4	0.073
Group IV			6.8	0.065	6.7	0.060	6.7	0.075	7.3	0.070

S.E. = Standard Error.

so consistent. Mull and Bill<sup>5</sup> report that the serum phosphorus decreases from 3.4 to 3.2 mg. per cent at the end of the second trimester. They consider this difference of 6 per cent as significant. In our control group, the average phosphorus concentration in the second trimester is 4.2 and in the third 3.4, a difference of 20 per cent and yet the individual variations are such that on statistical analysis this change is not significant. This drop in the third trimester, however, is not found in any except the control group. This control group shows a greater rise post partum than any of the other groups.

Although the effect of the added calcium and vitamins A and D was not apparent in the serum calcium and phosphorus of the mother, they did have an effect on one fetus. Patient (No. 170909) gave birth to a stillborn fetus. The mother had received 5,550 units of vitamin D daily for twenty weeks preceding the delivery and the fetus contained considerably more calcium and phosphorus than published figures for fetuses of the same age. This is in accordance with the work of Swanson and Iob<sup>10</sup> on rats, who found that the ash content of rat pups from mothers receiving viosterol had a calcium content 9 per cent greater and a phosphorus content 11 per cent greater than the ash content of the pups in the control group. When the mother rat was given cod liver oil the ash content of the offspring contains 10 per cent more calcium and 12 per cent more phosphorus than the ash content of the control group. Nicholas and Kuhn<sup>6</sup> also found an increased content of calcium in the bones of rat pups if vitamin D was given during pregnancy.

The hemoglobin concentration and hematocrit were determined in our various groups to see if there was any change which might be attributed to the therapy used. The data are given in Table III. In the first trimester of pregnancy the mean for hemoglobin was 12.2 Gm. per cent and for the hematocrit it was 38.2 Gm. per cent, results which are within the normal range. In the third trimester the mean for hemoglobin in the control group was 12.0 Gm. per cent and for hematocrit it was 35.2 per cent. The decrease is usually greater. This decrease begins in the first half of pregnancy, reaching a minimum about the thirtieth week, and then begins to increase up to term. The average decrease is 15 per cent.

The data for hemoglobin and hematocrit in the various groups can be seen to be quite similar. Even the groups that were given the added iron in the cereal did not show any marked variation in the hemoglobin concentration. This fact is in contradiction to some suggestions that the decrease in hemoglobin in pregnant women is due to the fetal needs for iron. The amount of iron necessary for fetal growth is negligible during the first 28 weeks of pregnancy and yet it is at this period that there is the greatest fall in the hemoglobin concentration. It is only during the last 12 weeks, when the fetal weight increases from approximately 1,000 Gm. at 28 weeks to 3,200 Gm. at term that the iron require-

ment of the fetus becomes appreciable. But even at term when the actual amount of iron required by the fetus is greatest it amounts to only 280 mg., which could be furnished by the iron from 600 c.c. of maternal blood. Yet it is at this latter period that the hemoglobin concentration seems to be stationary or is already increasing, so that during the maximal fetal requirements the maternal hemoglobin concentration also increases. In other words, the anemia of pregnancy does not seem to be due to the parasitic action of the fetus in removing iron from the maternal circulation.

There is a sharp rise in the hemoglobin and hematocrit concentrations post partum, but these are still a little below that reported for nonpregnant patients, perhaps because our results were only carried to a little more than six weeks after delivery.

The average serum protein concentration for normal individuals, based on reports in the literature, is 7.5, with a range from 6 to 8.3 per cent. The mean serum protein concentration in normal pregnant patients is 6.5 per cent. The data for serum proteins are presented in Table IV. The mean for the serum protein in the first trimester of pregnancy is 6.8 Gm. per cent, and the averages for the various groups at term are approximately the same. There is a decrease in the second trimester and an increase after delivery, but when treated statistically these changes are not found to be significant.

Some of the maternal conditions which have been reported as being prevented, improved, or cured by calcium and/or vitamin D administration are as follows: (1) tetany, muscle cramps and backache; (2) paresthesias, psychoses, irritability and insomnia; (3) eclampsia and pre-eclampsia; (4) edema; (5) hyperemesis gravidarum; (6) dental caries (improved in two weeks); (7) the coagulation time of the blood and blood loss of the third stage of labor; (8) thinning of hair; (9) varicosities; (10) friable perineum; (11) ante-partum phlebitis; (12) greater strength and well-being of the mother; (13) brittleness of nails; (14) duration of labor.

Some of the fetal conditions supposedly amenable to calcium and/or vitamin D administration are as follows: (1) intrauterine injuries; (2) neonatal rickets; (3) better teeth and jaws; (4) intrauterine bowing of legs disappears in one-fourth to one-half of the usual time; (5) the blood loss during circumcision is less.

Richardson<sup>5</sup> and others state that the administration of calcium or of vitamin D will decrease the blood loss during the third stage of labor. Our results show an almost identical blood loss in all four groups. No effect is shown by either the administration of calcium or vitamins A and D or both. Data are given in Table V.

Neither is the duration of pregnancy effected by the substances added to the diet. The mean for the duration of pregnancy in the control group was 40.1 weeks and the other three groups were essentially the same. The total weight gain in pregnancy varied considerably in the

TABLE V. VARIOUS DATA CONCERNING PREGNANCY

	GROUP I	GROUP II	GROUP III	GROUP IV
Deliveries—36 weeks	166	176	95	99
Babies—alive %	98	94	99	98
Babies—dead %	2	6	1	2
Deliveries—28 to 36 weeks	5	3	3	3
Babies—alive %	80	67	67	100
Babies—dead %	20	33	33	
Abortions—6 to 28 weeks	4	0	0	0
Duration of pregnancy—weeks	40.1 ± 1.9	40.2 ± 1.5	40.3 ± 1.8	40.5 ± 1.2
Total weight gain—kilo	9.6 ± 1.2	10.8 ± 4.2	11.1 ± 4.0	11.4 ± 3.9
Average gain per wk.—Gm.	478 ± 188	495 ± 187	474 ± 161	493 ± 154
Duration of labor—hours				
Primipara	13.0 ± 7.1	15.9 ± 8.5	13.4 ± 7.5	16.9 ± 10.3
Multipara	7.9 ± 4.2	9.3 ± 6.8	7.6 ± 4.6	8.6 ± 5.4
Blood loss—third stage c.c.	245 ± 153	238 ± 128	235 ± 126	242 ± 100
Time of onset of lactation, day	4	4	4	4

groups. The total weight gain for the control group was 9.59 kg. while each of the other three groups showed greater weight gains. These added gains in each of the three cases are significant. Just how to explain the increased weight gain is difficult especially in those who took the vitamins A and D. If a sufficient amount of the cereal was taken it could account for the increased weight gain. It may be that the ingestion of the special cereal or of the vitamins stimulated the appetite of the patients resulting in an increased ingestion of food. Our experience has been that the weight gain in pregnancy will amount to more than 10 kg. if the patients are left to their own choice of food, and it will be considerably more than 12 kg. if they are encouraged to eat and to drink large amounts of milk. The average gain per week for the control group was 478 Gm. and for Groups II, III and IV the means were similar.

The duration of labor for primipara in Group I was 13 hours which is much lower than the average 18 hours usually given in textbooks. Groups II, III and IV showed significant increases. The average duration of labor for multipara in Group I was 7.9, in contrast to the usual figure of twelve hours. The test groups showed no marked changes.

No real differences were shown by the groups with regard to abortions, premature and term deliveries and fetal mortality. In these instances the number of patients was so small that no conclusions can be drawn.

The incidence of some complications of pregnancy in the four groups studied are listed in Table VI. Some differences can be noted. In post-

TABLE VI. INCIDENCE OF COMPLICATIONS OF PREGNANCY—PER CENT

	GROUP I	GROUP II	GROUP III	GROUP IV
Toxemia	8.6	5.9	14.5	4.9
Abruptio placenta	0.6	0.6	1.0	0
Anemia	2.9	2.8	3.1	3.9
Pyelitis	0	1.7	0	2.9
Post-partum hemorrhage	7.4	3.4	3.1	3.9
Morbidity	12.0	9.5	21.9	13.7
Puerperal infection	8.6	3.9	5.2	2.0

partum hemorrhage and puerperal infection, the groups fed the special diets had a much lower incidence of both of these conditions than the control group. But we hesitate to claim any significance for them first, because we feel that for evaluating incidences of conditions the group should be much larger, and second, because on the same principle there would be discrepancies in the other figures that would be hard to explain. For instance, the higher incidence of toxemia and morbidity in Group III, the group that received the vitamins, is difficult to explain when Group IV, which received both the cereal and vitamins A and D, has a much lower incidence. The other conditions listed do not vary much.

Data pertaining to the fetus are given in Table VII. The average birth weight of the baby in the control group was 3,358 Gm. and the weights in the other three groups were essentially the same. The excessive weight gain of the mother in the three tests groups could not be attributed to increased fetal weight and must have been entirely maternal tissue. The initial weight loss in Group I was 197 Gm. and there was no change in any of the three groups. We have listed the percentage of cases in each group in which the babies were breast fed, complimented or supplemented. There are differences for the various groups and in some instances they are quite striking, but so many factors are concerned in the feeding of babies that we do not wish to draw any conclusions from the data. There are certainly no correlations between Groups II and IV, in which each patient received the special cereal, nor is there any correlation, insofar as breast feeding is concerned, between Groups III and IV, in which each patient received vitamins A and D. Furthermore, the extra weight gain of the mother in Groups II, III, and IV did not increase the number of cases of breast feeding in Groups II and IV but did in Group III.

TABLE VII. VARIOUS DATA CONCERNING THE BABY

	GROUP I	GROUP II	GROUP III	GROUP IV
Baby, birth weight—Gm.	3358 ± 547	3418 ± 467	3341 ± 526	3359 ± 456
Initial weight loss—Gm.	197 ± 92	209 ± 85	201 ± 86	202 ± 85
Type of feeding:				
Breast — %	35	48	32	15
Complementary— %	52	44	58	65
Supplementary — %	13	8	10	20

Considerable attention has been given to the relationship between calcium intake and the teeth of the mother and the baby, but especially the former because of the dictum "for every child a tooth." However, many physicians and dentists still advise their patients to take calcium to prevent tooth decay during pregnancy despite the well-known fact that once calcium is deposited in the teeth, it cannot be withdrawn. The amounts of calcium salts that are quite often prescribed yield a negligible amount of calcium. Thus, for one gram of calcium it requires



3.5 Gm. of the chloride, 4 Gm. of the acetate, 7.7 Gm. of the lactate, and 11 Gm. of the gluconate.

Oberst and Plass<sup>7</sup> recently reported their metabolic studies made on five pregnant patients who were kept in the hospital on adequate diets. A pertinent observation made by them was that "in no case did new dental caries develop." A consistent improvement in the teeth of the five patients was noted. This observation by Oberst and Plass has not been confirmed. The number of patients is very small and other factors have not been excluded.

Rickets in newborn and young infants has been reported but only if the maternal diet was markedly deficient in calcium and vitamin D.

The difficulty in determining the value in human beings of diets adequate in both food and vitamin content is illustrated by the following reports. Ross, Perlzweig, and co-workers<sup>9</sup> studied a group of pregnant women in an institution. One series for economic reasons received the general diet which was low in milk, butter, eggs, meat, fish, and fresh fruits. Another series had a well-balanced diet with adequate amounts of vitamins A, B-complex, D, and E, as well as calcium, phosphorus, and iron. They concluded that there was no significant difference between the two series as to the incidence of toxemia or concentration of hemoglobin and serum protein.

A preliminary report of the British Minister of Health stated that among 4,446 mothers receiving special food, the puerperal death rate was 0.45; the maternal death rate from associated causes, 0.67; and the infant death rate (stillbirth and neonatal), 54. Among 9,040 mothers not receiving special foods, the corresponding rates were 3.54, 1.33, and 83, respectively. A more careful analysis of the data by the committee indicated that the practical difficulties in the way of securing precise comparability between the contrasted groups, having regard to the number of possibly relevant factors (age, parity, diet, medical supervision, etc.) are so great that it is unlikely that scientifically adequate conclusions would be reached.

Ebbs, Tisdall and Scott<sup>3</sup> have studied the influence of the prenatal diet on both mother and baby. They found that there were more cases of anemia, toxemia, and threatened miscarriage in the poor diet group. The total number of complications in this group was almost double that in the group who had an adequate diet. However, their figures for hemoglobin concentrations, ascorbic acid and phosphatase show no significant differences for the patients on various diets. Likewise some of their figures for the complications of pregnancy either do not show significant differences or they are not consistent. Furthermore, since many of these complications have a very low incidence, the number of cases used for the study by these investigators is too small. More babies from patients who had been on a poor diet required artificial feeding and had more of the common complications that occur in the first six

months of life than babies from patients who have received a good diet. The authors concluded that their study suggested that the nutrition of the mother during the prenatal period influenced to a considerable degree the whole course of pregnancy and the health of the baby.

Williams and Fralin<sup>12</sup> analyzed the food intake at home of 514 patients and found that 58 per cent of the diets were poor, 40 per cent were fair and 2 per cent were good. They noted no evidence that toxemia occurred more frequently in the presence of insufficient protein, vitamin A or B intake. They stated that although their series was small, a deficient diet did not seem to be responsible for abortions, pyelitis, premature labor, stillbirths, etc.

Tompkins<sup>11</sup> in a preliminary report stated that the incidence of toxemia was almost seven times greater in patients on a deficient diet. The stillbirth and neonatal mortality rates were also much higher. The changes, however, are not significant. Furthermore, the patients in the "good" diet group were all given prenatal care by him while the deficient diet group was selected from the files of the hospital. The study would be of far more value if he had also given prenatal care to the patients in the deficient diet group.

The chief criticism of the reports by Ross and co-workers,<sup>9</sup> by Ebbs, Tisdall and Scott,<sup>3</sup> by Williams and Fralin,<sup>12</sup> by Tompkins,<sup>11</sup> by Burke and co-workers,<sup>2</sup> by us and by many other investigators is that there is no certainty that the patient ate the food which she said she did. We checked on several patients and found that the food actually eaten was always less in amount, quality and variety than stated by the patient. *Furthermore, no one has had a large enough number of patients to make any changes which occurred significant.* A larger number of balance studies, carried out under carefully controlled conditions, is necessary.

### Summary

We have followed a group of patients through pregnancy and the puerperium to determine if the addition of calcium, phosphorus, iron, or vitamins A and D to the diet had any effect on the course of pregnancy, prevented complications from developing, or insured a higher incidence of normal infants.

Studies of the serum calcium, phosphorus, and protein, as well as hematocrit and hemoglobin showed them to be within normal limits and uninfluenced by the foregoing additions to the diet.

A study of the effect of the additions to the diet on the various complications of pregnancy showed some differences but no definite conclusions could be drawn. The duration of labor was certainly not shortened by the administration of vitamin D as has been suggested. The additions to the diet caused a significant increase in maternal weight.

No significant effects were noted on the fetus that could be attributed to the changes in diet.

Unquestionably a proper diet predisposes to better health, to a normal pregnancy and to a healthy child, but we believe that the value of a diet can only be proved by prolonged studies of a large number of pregnant women in an institution.

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# THE RELATIONSHIP OF CONGENITAL SYPHILIS TO ABORTION AND MISCARRIAGE, AND THE MECHANISM OF INTRAUTERINE PROTECTION\*

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THREE decades ago<sup>1</sup> syphilis was considered to be one of the most frequent causes of repeated abortion and premature labor, and 25 years ago, Royston<sup>2</sup> concluded, from a study of 115 abortions in 51 luetic patients, that syphilis interrupts pregnancy at any and all periods of gestation and that syphilitic women abort more than 60 per cent of their pregnancies. More recently, McKelvey and Turner<sup>3</sup> found an abortion rate of only 5 per cent in a large series of luetic mothers, and today the consensus is that syphilis rarely, if ever, causes the termination of a pregnancy in its earlier months.

That syphilis is a factor to be reckoned with in the latter one-half of pregnancy was shown by Williams's<sup>4</sup> demonstration that lues was the etiologic factor in 40 per cent of the Johns Hopkins Hospital dead-horn premature infants, and in approximately 80 per cent of the macerated children. He<sup>5</sup> was unable to show that the *Spirochaeta pallida* infected the product of conception long before the period of viability had been reached. However, McCord<sup>6</sup> has said that he could see no reason why the organism of syphilis could not be found in early abortions and has continued extensive work along this line. It was on account of these differences that the present study was begun under the direction of the late Dr. J. Whitridge Williams.

The fetus of each patient who aborted on either the house (ward and private) or home delivery service, from February, 1931, through June, 1933, was carefully autopsied and certain internal organs sectioned and stained with the Levaditi stain for spirochetal organisms. Thereafter, and until the end of 1939, only those fetuses of mothers with syphilis were included in the study. Any patient with a positive blood Wassermann or with negative serology following antiluetic therapy was considered syphilitic. In each instance, utilizing Streeter's charts,<sup>7</sup> the anatomic age of the fetus was determined from its crown-heel and crown-rump lengths, preference being given the latter in the event of different estimates of gestational age. When available, the menstrual age was used for purposes of comparison and for estimating the period of retention after fetal death.

A diagnosis of fetal syphilis was made only when spirochetes, as shown by the Levaditi stain, were found in the fetal organs. Evidence

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has accumulated to show that there is no other reliable criterion for this diagnosis. Thus, Caffey<sup>8, 9</sup> has conclusively demonstrated that many of the x-ray findings formerly ascribed to syphilis of the long bones may be duplicated by other diseases or may represent the deposit of some heavy metal, as bismuth, used in antisyphilitic treatment of the mother. The role played by bismuth in this respect has been confirmed by Whitridge.<sup>10</sup> The work of Christie<sup>11</sup> and others has shown that even the positive quantitative Wassermann reaction obtained from cord blood is not pathognomonic of fetal syphilis, for the number of circulating units of reagin in the bloods of mother and fetus are essentially the same. Similar tests must be repeated at intervals upon the infant's blood before one can be certain, from serology, that the infant is manufacturing its own reagin. Williams<sup>4</sup> and McKelvey<sup>3</sup> have pointed out the dangers in attempting to diagnose congenital syphilis from the microscopic appearance of the placenta alone. And McCord<sup>12</sup> has found that the difficulties in diagnosing placental syphilis become increasingly more so the farther from term the product of conception is expelled. The failure to demonstrate spirochetes in dark-field examination of fresh scrapings from the wall of the umbilical vein does not rule out fetal syphilis. Furthermore, Siddall<sup>13</sup> has found that perivascular round-cell infiltration of the umbilical vessels is not pathognomonic of luetic infection of either the fetus or the funis. There remain, then, only careful pediatric follow-up in liveborn fetuses, and the presence of spirochetes in autopsied material as reliable criteria for the diagnosis of congenital syphilis.

A careful and systematic search for spirochetes was made in sections of liver, lung, adrenal, pancreas and kidney obtained from every fetus and stained by the Levaditi method. These internal organs were selected for study since Tissier and Girauld<sup>14</sup> reported finding the parasites in luetic fetuses most abundant in the adrenals, occurring there in 97.5 per cent of all cases and progressively less common in the lungs, pancreas, and liver. The placenta was not routinely examined for spirochetes in this study on account of the previous reports by Trinchese<sup>15</sup> and Pauli<sup>16</sup> who state that it may be necessary to examine several hundred sections before the typical but sparsely scattered organisms may be recognized with certainty. The kidneys were not found to be desirable organs for the search of the parasites. The occasional section of umbilical cord and long bone, likewise, never contained as many organisms as the other tissues; and frequently no typical parasites were recognized in bone or funis although they were found in great abundance in liver, lung, and pancreas.

No special count of spirochetes was made in any of the organs but rough comparisons were made. No uniformity in preponderance of organisms was found in any particular internal organ examined, such as noted by Tissier and Girauld.<sup>14</sup> Generally, however, they were

present in largest numbers in the perivascular tissues of liver and lung.

The characteristic morphology of the *Spirochaeta pallida* was not found in three macerated fetuses from missed abortions. In each one of these the very great majority of suspected spirochetes were relatively short, stocky, and contained few or no undulations, and were associated with large numbers of granules staining readily with the silver preparation. McCord<sup>17</sup> too, found great variations in the morphology of the spirochetes in macerated fetuses and particularly those syphilitic fetuses from luetic mothers who had negative blood Wassermann reactions. At the time we first noted these, the suggestion was that they represented dead or dying spirochetal organisms. This was confirmed by observing a fresh dark-field specimen and following the morphological changes associated with aging of the preparation. In both instances, the abnormal forms noted were similar to those described by Warthin and Olsen<sup>18</sup> as atypical spirochete forms. The question of whether these were involutional or evolutionary forms was left open by them.

The literature contains no specific data to indicate that *Spirochaeta pallida* will not continue to live indefinitely in the organs of a dead fetus, the temperature of which is maintained at normal body levels, as occurs in retention in utero. Adair and Schumann<sup>19</sup> do say that the spirochetes seem to disappear rapidly from dead tissues unless incubated, and Gellhorn<sup>20</sup> that spirochetes seem to multiply and may retain their virulence as late as three days after death. It is known, also, that anyone handling syphilitic cadavers runs the risk of luetic infection and Hoffmann<sup>21</sup> in 1927 considered 20 of the 38 reported cases as authentic. In 15 of the 20 cases, the primary lesion followed autopsies on luetic children and fetuses, all of which came to post-mortem examination within 24 hours after death or delivery. Grigoviev and Jarysheva<sup>22</sup> have proved that the spirochetes may live for some days in tissues that are kept in a refrigerator for they were able to successfully infect rabbits from inoculated pieces of liver, placenta, and umbilical cord of a macerated syphilitic fetus after as long as 48 hours of refrigeration. A few spirochetes remained alive after the tissues had been kept on ice for six to 10 days but inoculations as late as this gave negative results.

### Present Study

For purposes of this study, the gestational periods are divided into groups comparing more nearly to the strict medical definitions of abortion and miscarriage rather than to the more loose medical terminology, i.e., abortion will refer to pregnancies terminating before the end of the seventeenth gestational week, and miscarriage between this period and the onset of the twenty-eighth week. The miscarriage group will be further divided into early and late subgroups.

In the first part of the study, in which fetuses of both luetic and nonluetie patients were included, there were 68 fetuses from 66 nonluetie mothers. Two women accounted for four fetuses, each woman giving birth to monozygotie twins. The anatomic ages of these 68 fetuses ran from eight to 27 weeks with the distribution shown in Fig. 1. One fetus presented many small but macroscopic pulmonary cysts. No other congenital anomalies were found but in two instances a true knot of the umbilical eord, which was tightly drawn, might have accounted for the fetal death. With one exception, all were intrauterine pregnancies. Forty fetuses were males and 28 females, a sex ratio of 143 which compares favorably with all earlier statistics which show a sex ratio in abortions higher than the usual birth ratio of 106 males to 100 females. Thirteen fetuses (nine females and four males) were macerated; six of these were badly macerated (four females and two males) and all were apparently authentic cases of missed abortion, with one dead fetus retained in utero for 11 weeks.

No spirochetes were found in any of these 68 fetuses of nonluetie women. This should overrule the objection that if spirochetes were found in the fetuses of luetic mothers, such spirochetes might well be nonspecific organisms.

During the same period in which the above 68 nonluetie fetuses were collected, the pregnancies of 21 syphilitic women terminated in abortion or misearriage. In the latter part of the study, 46 fetuses were added for a total of 67 fetuses of luetie mothers. The distribution of anatomic ages of these fetuses is included in Fig. 1. One nonmacerated fetus presented bilateral macroscopic pulmonary cysts and no spirochetes were located in its tissues. There were no other congenital anomalies. Two women delivered twins of the dizygotie variety and not one of these four fetuses was syphilitic. Twenty-six (16 males and 10 females) or 38.8 per cent of the 67 fetuses were macerated and six cases were considered cases of missed abortion (four male and two female) with periods of retention ranging from four to 17 weeks. The distribution between sexes was 31 males and 36 females, a sex ratio of 86 which is far below the usually quoted birth sex ratio of 106 and the abortion ratio of 120 males to 100 females. This is in contradistinction to a high sex ratio, 171, found in syphilitic fetuses succumbing in utero after viability has been reached.<sup>23</sup> A similarly high sex ratio, 162, was noted<sup>23</sup> in neonatal deaths due to congenital syphilis. There was no ready explanation for these paradoxical apparent susceptibilities of the viable male fetuses or newborn infants of luetic mothers. The high sex ratio in this latter group is more in keeping with the well-recognized relatively greater immunity of the female to this infection than the male possesses.<sup>24</sup>

On the basis of the presence of organisms morphologically like those of *Spirochaeta pallida*, a diagnosis of fetal syphilis was made in 16 of

the 67 fetuses of luetic mothers who aborted or miscarried, an incidence of 23.88 per cent. Further breakdown reveals that spirochetes were found in 14 of the 42 fetuses of Wassermann positive mothers, 33.3 per cent, and in two of the nine from Wassermann negative mothers, or 22.2 per cent. This confirms the fact that serology rendered negative by antiluetic therapy is no safeguard against congenital syphilis in a subsequent pregnancy. The usually quoted incidence of con-

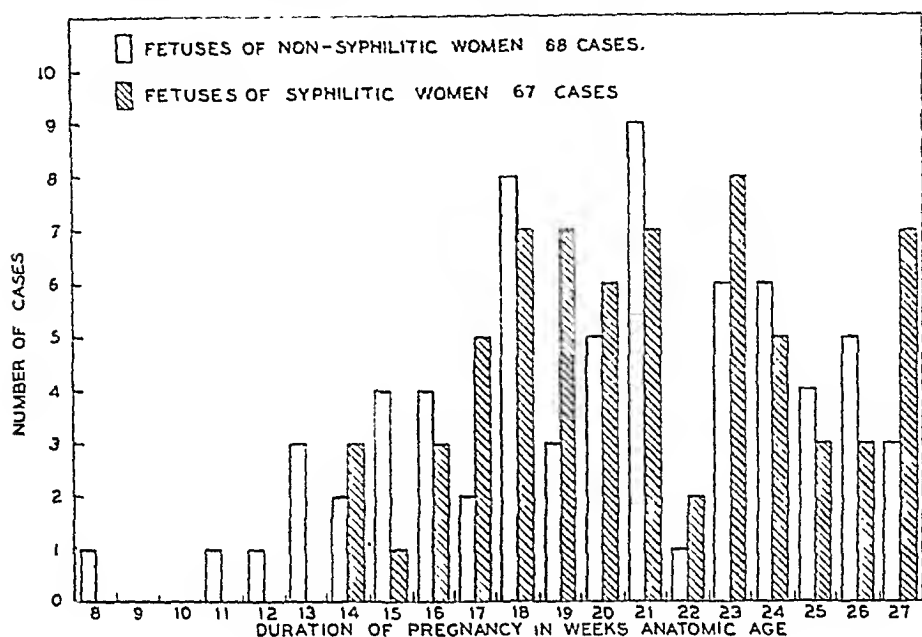


Fig. 1.—Distribution of fetuses of syphilitic and nonsyphilitic women according to anatomic age.

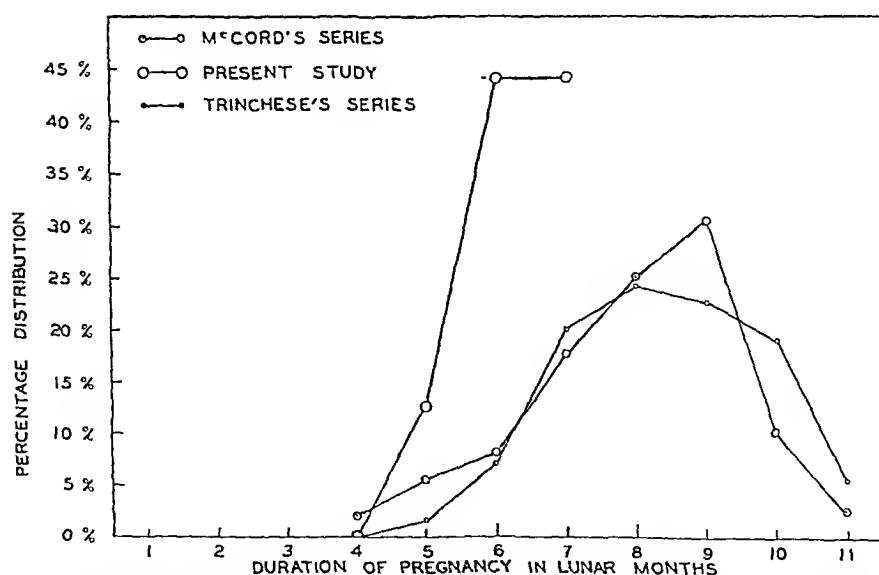


Fig. 2.—Percentage distribution of syphilitic fetuses according to lunar months gestation and expressed in percentage of the total number of fetuses in each study.



genital lues in Wassermann negative mothers is 10 per cent, i.e., one-tenth of all congenital luetics are born of Wassermann negative women. The number of fetuses with spirochetes is too small to show as a significant statistical graph if presented according to weeks gestational age, so they are grouped, in Fig. 2, according to lunar months gestation. The cases of this study are compared in the same figure with a curve reported by Trinchese<sup>15</sup> and with another curve obtained from McCord<sup>17</sup> by converting his fetal weight figures into comparable anatomic ages. This conversion cannot be considered highly accurate since McCord gives no information on prescenee and extent of maceration or on periods of retention in utero.

The series are not entirely comparable since Trinchese<sup>15</sup> and McCord<sup>17</sup> include fetuses of all gestational ages, whereas our series includes none advanced to viability. McCord<sup>17</sup> includes some cases in which syphilis was diagnosed on the basis of x-ray findings of the long bones, whereas the criterion for fetal syphilis in the other two studies was the presence of spirochetes in fetal tissues. Moreover, since McCord's figures were obtained by converting birth weights to gestation ages, the resultant figures are probably too low because there must have been maceration and varying periods of intrauterine retention with some soft tissue absorption. However, it is significant that fetal syphilis was never diagnosed before the sixteenth week of gestation in any one of the three studies which represent a total of more than 200 syphilitic fetuses. Actually the earliest gestational age in which spirochetes were known to have been found in fetal tissues was 18 weeks—present series and Trinchese.<sup>15</sup>

The current series is shown in Fig. 3, where the total number of fetuses from luetic mothers is plotted with the number of fetuses showing spirochetes in each age group. It will be seen that spirochetes were not encountered in 12 fetuses which were expelled or died in utero at anatomic ages ranging from the fourteenth through the seventeenth weeks of gestation. Roughly 10 per cent of the 29 fetuses from the eighteenth through the twenty-second gestational weeks were infected, whereas the incidence of infection in the late miscarriage period was 50 per cent, with the highest rate, 66.7 per cent, in the twenty-sixth week. While the number of cases observed is not large enough to make the resultant figures statistically reliable, they certainly do indicate that abortions are rarely, if ever, the direct result of fetal syphilis; that syphilis is occasionally responsible for interruption of pregnancy in the first one-half of the miscarriage period, and may frequently be responsible for such an outcome in the latter part of the miscarriage period. A careful analysis of these fetuses with spirochetes, the associated placentas, and the mothers would be essential to a determination of whether such factors as antisyphilitic treatment and blood Wassermann reaction are correlated with the above figures.

The occurrence of spirochetes in fetuses in the three divisions of the previsible period, as previously indicated, is compared in Fig. 4, with the maternal blood Wassermann reaction on the one hand, and with the amount of antiluetic treatment given the mother during the current pregnancy on the other. No cases had adequate antisypilitic therapy<sup>3</sup> for none received as much as four grams of arsphenamine or its equivalent, or as many as 12 treatments of an arsenical. In Fig. 4,

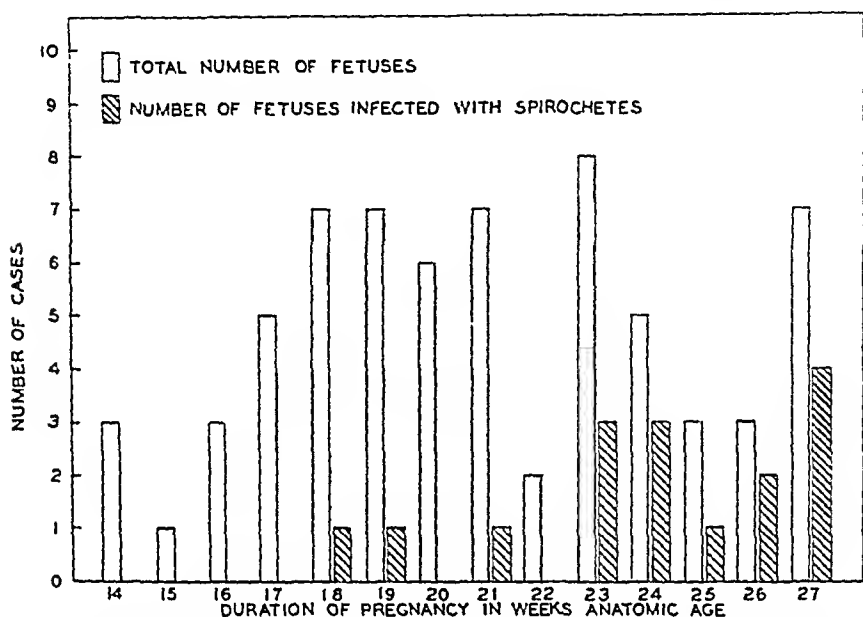


Fig. 3.—Distribution of total number of fetuses of luetic mothers and those fetuses in which spirochetes were found grouped according to anatomic age.

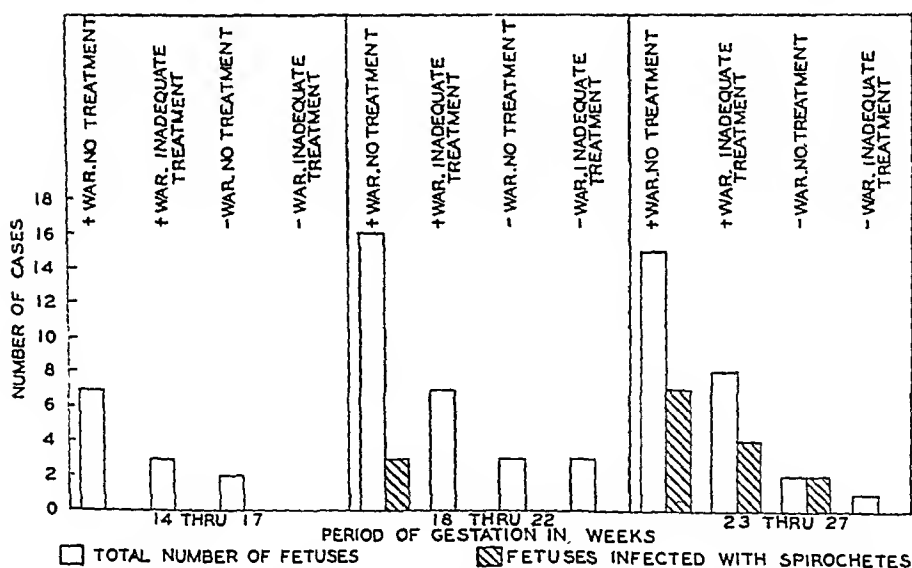


Fig. 4.—Distribution of total number of fetuses of syphilitic women and those fetuses infected with spirochetes grouped according to fetal age and correlated with the blood Wassermann reaction and with antiluetic treatment given the mothers in the current pregnancy.

it is suggested, from our limited experience, that the chances of fetal infection with spirochetes are nil irrespective of whether the maternal blood Wassermann is negative or positive or whether the mother has or has not had antiluetic treatment when she aborts or her fetus succumbs in utero before the eighteenth week of gestation. However, it seems clear that the Wassermann positive luetic mother must be given some arsenic therapy before the eighteenth week of gestation if syphilitic infection of her fetus is to be certainly avoided. Moreover, apparently some arsenic therapy, however inadequate it may be, if given before the eighteenth week, will tend to protect the fetus from the invasion of *Spirochaeta pallida* but will not preclude the infection if therapy is inadequate. Furthermore, it seems certain that some antiluetic treatment must be given before the twenty-third week of pregnancy, irrespective of whether the maternal serology is negative or positive, or luetic infection of the fetus must be anticipated in at least 50 per cent of the cases terminating before the twenty-eighth week. These inferences confirm the modern view that antisyphilitic treatment in the form of an arsenical should begin in pregnancy just as soon as syphilis is diagnosed and not delayed even to the twentieth week of gestation as some advocate.

It has been postulated that the reason for the greater incidence of syphilitic infection of the fetus in the advanced pregnancy as against that of the pregnancy in progress for less than 16 weeks, is the greater period of time in which the chorionic villi have been exposed to the maternal infection by being bathed in blood containing the organisms. To this theory, Trinchese<sup>15</sup> has added the fact that the arborescence of the villi becomes tremendously increased as gestation advances so that at midpregnancy the surface area of the placental villi is several thousand times as large as in early pregnancy. He concludes that the possibility of fetal infection with the *Spirochaeta pallida* through the maternal blood rises in the same ratio as the increase in surface area of chorionic villi. But this latter theory, of course, is not literally tenable.

The early fetal protection from the invasion of the maternal spirochetes must be viewed from other angles. Beck and Daily<sup>25</sup> have set forth several sound lines of reasoning. Among these, they argue that the Langhans cells, as long as they are alive and vigorous, undoubtedly act as an efficient barrier to the invasion of spirochetes. It is a well-known fact that the Langhans layer of chorionic epithelium does not normally persist as an intact layer after the sixteenth week of pregnancy. The absence of fetal syphilis before this time and its increasing incidence for approximately 16 weeks thereafter is certainly strongly suggestive evidence of the protective properties of these cells which themselves, or through some product metabolized by them, have the capacity to erode and to invade. The disappearance of the Langhans

layer of epithelial cells is by no means a regular occurrence and various degrees of its persistence may be observed long after the usual time for its disappearance. Near-term, and even term placentas as well, occasionally present this phenomenon which Hertig<sup>26</sup> has designated as delayed delamination and differentiation. The incidence of this phenomenon is not known. But, if the theory of Beek and Daily<sup>25</sup> is correct, we should expect to find a lower incidence of spirochetal infection of the fetus in association with those placentas which show evidence of delayed delamination and differentiation than in those not showing persistence of the Langhans cells.

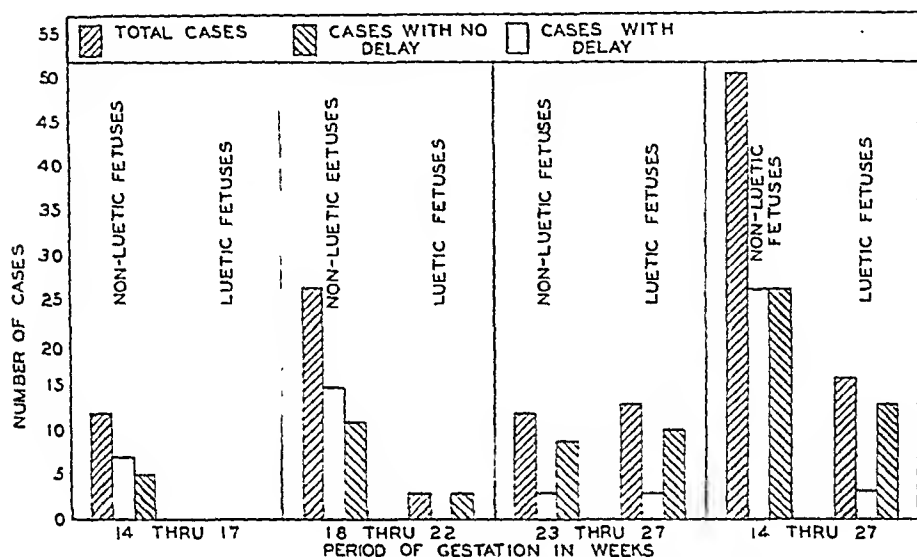


Fig. 5.—Distribution of total number of fetuses of luetic women and those fetuses with and without congenital syphilis correlated with the absence or presence of evidence of delayed delamination and differentiation of the Langhans layer in the corresponding placentas.

Our luetic patients whose fetuses contained spirochetes associated with and not associated with placentas showing some delay in delamination and differentiation are given in Fig. 5. Here it is seen that 50 per cent of the noninfected fetuses of syphilitic mothers were associated with placentas showing evidence of delayed delamination and differentiation whereas the corresponding figure for fetuses showing spirochetes was only 18.75 per cent. We must conclude, then, that the Langhans cells do afford a measure of protection to the fetus against the maternal luetic infection. Moreover, no patient received more than one-third the amount of arsenic therapy considered necessary to afford minimum protection to the fetus and there is then no apparent explanation for the intrauterine protection other than the Langhans layer of chorionic epithelium. Further observations along these lines are strongly indicated.

### Conclusions

1. A series of 68 fetuses of nonsyphilitic and 67 of luetic women were autopsied and certain tissues searched for the presence of spiro-

chetes. Only fetuses which had not reached viability were included in the study.

2. Fetal syphilis was diagnosed upon the discovery of spirochetes in fetal organs. No other criterion was considered reliable for the diagnosis from autopsy material.

3. Spirochetes were generally found in largest number in the perivascular tissues of liver and lungs. Long bone, placenta, and umbilical cord were least satisfactory for the search of spirochetes.

4. The characteristic morphology of the *Spirochaeta pallida* was not found in three macerated fetuses from missed abortions. That the observed structures were dead or dying spirochetes was proved by comparison with the changing morphology in an aging dark-field preparation.

5. No spirochetes were found in the stained preparation from the 68 fetuses of nonsyphilitic women.

6. Spirochetes found in the tissues of fetuses from luetic mothers (cases in which the blood Wassermann was positive as well as those in which serology had been rendered negative by therapy) were morphologically like the *Spirochaeta pallida* and were considered as such since no spirochetes of any form were seen in the fetuses of nonluetic mothers.

7. Spirochetes were found in 16 of the 67 fetuses of luetic mothers, an incidence of 23.9 per cent, which is the demonstrable role played by syphilis in the production of abortion and miscarriage in this series.

8. Spirochetes were discovered in 14 of 42 fetuses of Wassermann positive mothers, or in 33.3 per cent, and in two of nine fetuses of Wassermann negative mothers, 22.2 per cent, reaffirming that negative serology following antiluetic therapy is no assurance against congenital syphilis.

9. Spirochetes were not found in fetal tissues prior to the eighteenth week of gestation, i.e., in the abortion period. The incidence of fetal infection with spirochetes was found to rise from 10 per cent in the first one-half of the miscarriage period to 50 per cent in the latter one-half of that period with the highest incidence (66.7 per cent) in the twenty-sixth week. Appropriate conclusions relative to the role played by syphilis in terminating pregnancies before viability are drawn.

10. The limited material of this study suggests that there is some natural protection of the fetus against syphilis during the first 17 weeks of pregnancy. However, Wassermann positive mothers must receive therapy before the eighteenth week if their fetuses are to be guarded against syphilitic infection, and both Wassermann positive and negative grvida must have therapy before the twenty-third week or approximately 50 per cent of their fetuses can be expected to be infected before viability is reached. This confirms the modern teaching that anti-syphilitic treatment must be started early in pregnancy and certainly before the eighteenth week of gestation.

11. Evidence is offered to show that the Langhans layer of chorionic epithelium affords appreciable protection of the fetus against the invasion of the *Spirochaeta pallida*, even after the sixteenth gestational week. At this late stage it is in the form of delayed delamination and differentiation of the Langhans cells.

Acknowledgment is hereby given Mrs. Virginia Poor Walton, Technician for the Pathology Laboratory of the Department of Obstetrics, Johns Hopkins Hospital, for diligence in preparing a fine quality of Levaditi stained sections for this study.

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## MYOMETRIAL HYPERTROPHY (SO-CALLED FIBROSIS UTERI)\*

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PATIENTS suffering from uterine bleeding associated with a symmetrically enlarged, thick-walled uterus with little or no endometrial hypertrophy are quite frequently seen in the gynecological clinic. Various diagnoses have been applied to these uteri: fibrosis uteri, chronic metritis, arteriosclerosis uteri, metrorrhagia myopathica, etc.

The symptomatology and the clinical appearances have been well described by many writers as far back as Scanzoni<sup>1</sup> in 1863. There has been, however, wide difference of opinion both as to the pathologic processes involved and the etiology of this condition. The writers feel that they are able to present a clear picture of the histological findings without, however, being entirely certain of all the etiologic factors.

The material studied in this investigation consisted of ten uteri removed in patients upon whom a clinical diagnosis of fibroid tumor had been made. At operation, however, the uterus was found to be symmetrically enlarged with thickened walls but without localized tumor formation.

The clinical picture was quite clear cut. The patients ranged in age from 37 to 51 with one exception. This exception was a woman of 25 who had previously undergone a double salpingectomy with conservation of the ovaries, for pelvic inflammation. It would seem, therefore, that this condition was very nearly confined to the premenopausal decade.

All were multiparous women; two had borne six children each, one four, three two, one a single child, and one was merely stated to have been a multipara.

The symptoms in each case were prolonged uterine bleeding extending beyond or occurring between the normal menstrual periods, but not excessive in amount. The history most frequently given was a prolonged but not profuse flow often beginning with a menstrual period commencing slightly earlier than the expected date and continuing for two or three weeks up to entrance to the hospital. One patient had suffered from a profuse flow every two weeks for five years, and one had been treated for a similar episode two years previously with temporary relief. Most of the patients came to the hospital quite early for their abnormal bleeding.

\*Read at a meeting of the Obstetrical Society of Boston, April 20, 1943.

Seanzoni<sup>1</sup> described the symptomatology and gross appearances of this condition quite accurately in 1863. However, he scorned the microscope as a new fangled instrument which was quite useless to a clinician. Seanzoni, as did many after him, thought the condition he found to be chronic inflammatory in origin and called it chronic metritis.

Lorenz<sup>2</sup> from Theilhaber's clinic in Munich described under the name chronic metritis nine cases in considerable detail. He thought that he had demonstrated an increase in the fibrous tissue elements of the uterus and his article was illustrated by several beautiful plates. However, at that time (1903) he did not have available the more recent connective tissue strains.

Soon after the turn of the century the term chronic metritis was discarded for the newer concept of "fibrosis uteri." In 1915 Berkeley and Bonney<sup>3</sup> wrote of "fibrotic metritis" a disease in which the muscle of the uterus is largely replaced by fibrous tissue.

Blair-Bell<sup>4</sup> in 1917 applied the term fibrosis uteri to the large hard uterus often found in women 35 to 40 years of age. He observed that these women had the symptoms of leucorrhea, menorrhagia and occasionally metrostaxis. Histologically he said that the walls of the uterus were largely composed of fibrous tissue. He observed that the endometrium showed glandular hypertrophy, the glands being large and dilated, a condition almost invariably associated with bleeding. Blair-Bell attributed the conditions which he described to uterine infection subsequent to parturition.

Martin<sup>5</sup> and Reinecke<sup>6</sup> described arteriosclerosis of the vessels of the uterine wall and thought that this was the primary cause of the pathology present in these uteri. Palmer Findlay,<sup>7</sup> however, in an extensive analysis of the literature and from his own observations refuted the idea that arteriosclerosis was the essential pathologic process. He, however, also believed that an increase in fibrous tissue was the chief lesion to be found.

There were others who described hypertrophy of the muscular element of the uterine wall. Apparently the first of these was Klebs<sup>8</sup> in 1870. In 1907 W. Fletcher Shaw<sup>9</sup> made a careful microscopic study of 38 uteri which had been extirpated for what he termed "chronic metritis" and concluded that these uteri showed a simple hypertrophy of the myometrium and not a connective tissue hyperplasia. The percentage of connective tissue in the uterine wall he stated varied but the average amount was not over 0.8 per cent higher than in normal parous uteri.

Present day gynecologic writers, preoccupied perhaps with the fascinating study of hormonal changes in the endometrial cycle and their relation to abnormal bleeding, have ignored the existence of pathologic changes in the muscular portion of the uterine wall. Novak,<sup>10</sup> however, mentions both fibrosis uteri and hypertrophy of the uterus as poorly defined terms which both gynecologists and pathologists will differ in their use of, some not recognizing that such conditions exist.

It will be seen as the microscopic studies made by one of us (T. D. Kinney) are described that Klebs<sup>8</sup> and Shaw<sup>9</sup> were essentially correct in their observation. Before proceeding to these, however, a brief summary of the symptoms and clinical findings in each case will be given.



### Clinical Histories

CASE 1.—(Hospital No. 962952.) Mrs. A. G., was admitted on November 11, 1939. Contrary to the following cases, this patient had suffered some diminution in her menstrual flow but on examination by her physician a diagnosis of uterine fibroid had been made and the patient referred to the hospital. She was 45 years old, married and had given birth to three children normally. Her past history was otherwise negative.

Examination showed a large symmetrical uterus which was also diagnosed as a leiomyoma probably of the submucous type on admission to the hospital. A hysterectomy was performed on December 6, and a large thick-walled, symmetrical uterus was found with no local tumor formation. The patient made a good postoperative recovery for seven days, running a normal temperature and having no distention. On the morning of the eighth day, she was suddenly attacked with precordial pain and died in a few minutes. Autopsy permission was refused. A diagnosis of coronary embolism probably was made.

CASE 2.—(Hospital No. 976305.) Mrs. C. M., was admitted on March 21, 1940. She was a 39-year-old widow who had given birth to two full-term children, the first delivered by forceps, the second normally. She had had no serious illnesses or surgical operations.

For a year and a half before admission she had noticed some staining between periods and a distinct increase in the regular menstrual flow. Examination showed a symmetrically enlarged uterus which was removed by hysterectomy on March 23. She made a good recovery from the operation and was discharged on the twelfth day.

CASE 3.—(Hospital No. 1019889.) Mrs. A. J., was admitted on April 3, 1940. She was a 49-year-old married woman. The hospital record states that she was a multipara but the number of children to whom she had given birth was not mentioned. Previous history showed that in 1934 she had been operated upon for retroversion, a uterine suspension having been performed and the appendix removed.

Her catamenia were regular and normal and her chief complaint was a bearing down sensation in the pelvis, especially when on her feet. An enlarged prolapsed uterus was found and also a relaxed vaginal outlet. The uterus was removed by supravaginal hysterectomy and subsequently a repair of cystocele and rectocele performed. She made a good recovery and was discharged in good condition.

CASE 4.—(Hospital No. 976789.) Mrs. H. C., admitted on April 9, 1940. This patient was a 51-year-old married woman who had had six normal deliveries, the last one twelve years previously. An appendectomy had been done 22 years before entrance to hospital.

Her menstrual life had begun at 14, and had been regular and normal up to one month before admission when two weeks after completing her regular menstrual period, she started to flow again and continued to flow profusely for three weeks, at which time she entered the hospital.

On examination she was found to have a symmetrically, slightly enlarged uterus which was removed on April 27. She made a good postoperative recovery and was discharged on the twelfth day.

CASE 5.—(Hospital No. 975123.) Mrs. I. C., was admitted on March 12, 1940. She was a 46-year-old married woman who had had four full-term normal deliveries and one miscarriage. She had also been operated upon for removal of an ovarian cyst two years before admission. Menstrual history had always been regular at 28-day intervals but from 7 to 10 days in duration.

Three weeks before admission she had started to menstruate apparently normally but continued to flow freely up to the time of entrance to the hospital. Examination showed a moderately enlarged, symmetrical uterus.

A hysterectomy was done on March 12, and a thick-walled, symmetrical uterus was removed. She made a good convalescence and was discharged on the twelfth postoperative day.

CASE 6.—(Hospital No. 1015051.) Mrs. R. T., was admitted on February 2, 1941. She was a 25-year-old married woman who had given birth to two children normally. Her past history also revealed an appendectomy in 1935, an operation for osteoma of the thigh in 1936, and in 1939, a dilatation and curettage and a bilateral salpingectomy.

Since the birth of her last child seven years before she had suffered bilateral low abdominal pain and metrorrhagia and menorrhagia. The dilatation and curettage performed two years before had not relieved this nor had the bilateral salpingectomy.

The uterus was found to be symmetrically enlarged and was removed by supravaginal hysterectomy. She made a good recovery from operation and was discharged on the twelfth day.

CASE 7.—(Hospital No. 1040816.) Mrs. G. W. D., was admitted August 19, 1941. This patient was a 37-year-old divorced woman who had had one normal delivery and no surgical operations or serious illnesses. Her menstrual life had begun at 16; catamenia had varied in intervals from 21 to 28 days, five to six days in duration, with first-day pain up to the present illness.

Her present illness began seven years before admission with the menstrual periods starting six to seven days early, becoming more profuse in amount and with some intermenstrual bleeding. She had bled profusely for 9 days before entrance.

Examination showed a slightly enlarged, symmetrical uterus. She was curetted immediately upon entrance because of the severity of the flow. Six days later, on August 25, a supravaginal hysterectomy was done. Following operation the patient ran an elevated pulse and temperature with increasing abdominal distention and vomiting. She died on the third day of a fulminating general peritonitis.

CASE 8.—(Hospital No. 1039070.) Mrs. J. F., was admitted on September 9, 1941. This patient was a 46-year-old married woman who had given birth to six full-term babies normally. She had undergone three operations for osteomyelitis of the leg in childhood and had had a kidney operation. Her menstrual life had begun at 14 and had been normal up to 5 years before entrance to the hospital.

Since the birth of her last child five years previously, her catamenia had occurred every two weeks and had been profuse and prolonged and somewhat painful. The uterus was symmetrical and was estimated to be about two and one-half times normal size.

A hysterectomy was done and after a somewhat prolonged convalescence due to wound infection the patient was discharged on October 10, 1941.

CASE 9.—(Hospital No. 796589.) Mrs. A. D., was admitted on September 11, 1941. She was a 46-year-old married woman who had had three normal full-term deliveries. Her appendix had been removed in 1936. Her menstrual life had begun at 15 and had never been regular in occurrence but had been normal in amount.

Three weeks before admission she began to bleed one week in advance of the expected date of menstruation and had continued to flow moderately until coming into the hospital. Examination showed a slightly enlarged symmetrical uterus. This was removed by supravaginal hysterectomy from which the patient made an excellent recovery and was discharged on the twelfth day.

CASE 10.—(Hospital No. 1042899.) Mrs. M. C., was admitted on August 13, 1941. This patient was a 48-year-old married woman who had given birth normally to three full-term babies. In 1925 she had undergone a suspension of the uterus and appendectomy, and in 1940 a perineorrhaphy. Her menstrual life had begun at 12 and had been normal and regular up to the present flow.

Beginning with the regular time for the onset of menstruation she had started to flow profusely and continued for 14 days up to admission to the hospital. She was bleeding from the uterus quite freely on entrance. The uterus was enlarged and symmetrical. It was removed by supravaginal hysterectomy on October 16 and the patient made a good recovery and was discharged on the eleventh day.

### Pathology

The uterus in these cases presented a rather uniform picture. The most striking feature was the thickness of the uterine wall. In the present series of ten cases, the width varied from 1.6 cm. to 3 cm., while the average thickness was 2.3 cm. This was particularly striking when it is remembered that the normal uterine wall averages 1 cm. in thickness. The uteri were enlarged in these cases and the average size was 8.2 by 6.1 by 4.2 cm. exclusive of cervix. This again should be contrasted with the normal figures of 5 by 4.4 by 2.2 cm. The wall itself appeared on gross examination to be quite firm and pale, and pink-white in color. The endometrium did not appear to be grossly altered, and measured from 1 to 3 mm. in thickness, apparently depending upon the phase of the endometrial cycle.

On microscopic examination, the usual layers of the myometrium could be distinguished, i.e., the stratum submucosum, the stratum vasculare, the stratum supravasculare, and the stratum subserosum, and could usually be identified without difficulty. When the structure was studied in detail, the muscle fibers appeared larger than in the normal uterus.

The width of muscle fibers in the uterus in the present series was measured. These sections, as well as the sections in the control groups,

were fixed in alcohol-formalin and stained with hematoxylin and phloxine. It was felt that while some shrinkage of the muscle fibers would occur from the use of the fixative, and that the measurements of the muscle fibers obtained would be relative ones and not true measurements, the same factors would be present for both the present group

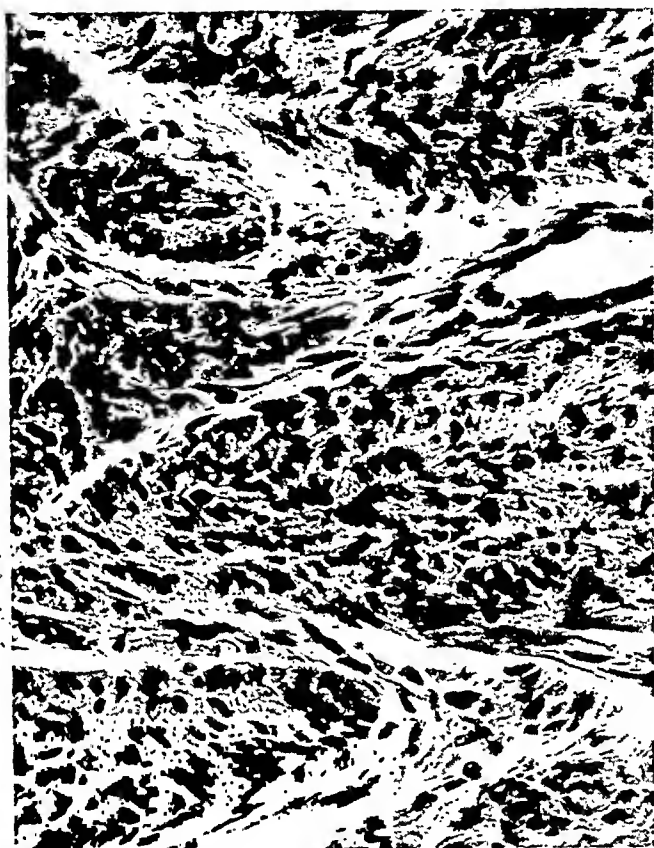


Fig. 1.—Section of normal uterine wall. Hematoxylin and eosin stain.  $\times 700$ .

and the control group. In measuring the muscle fibers an effort was made to use consecutive fibers whenever they could be identified. While there was a wide variation in the width of the individual fibers, the average width of the muscle fibers of the uteri in this series varied from 4.81 to 6.17 microns in width.

A control group of negative uteri from patients in the similar age group was studied. The average width of the muscle fibers in individual uteri in this series measured from 3.36 to 4.35 microns in width. In other words, the average width of the muscle fibers in this group of uteri was 2.22 microns greater in width than those in the control uteri. The number of muscle fibers was counted in both cases under consideration and the control series. In the latter group, the average number of fibers in individual uteri varied from 10.7 to 16.6 fibers per unit, measured on an average of 14 muscle fibers per unit for the con-

trol series. In the former group of cases, the number of fibers in individual uteri varied from 10.2 to 17.6 muscle fibers per unit, while the average number per unit for this group was 13.7. In brief, there appeared to be no significant difference in the actual number of muscle fibers present.

Sections were stained with Mallory's aniline blue and van Gieson's stain, in an effort to determine if the interstitial fibrous tissue of the myometrium was increased. It was concluded there was no definite increase in the fibrous tissue. There was no increase in the number of blood vessels, although the vessel walls were somewhat thickened.

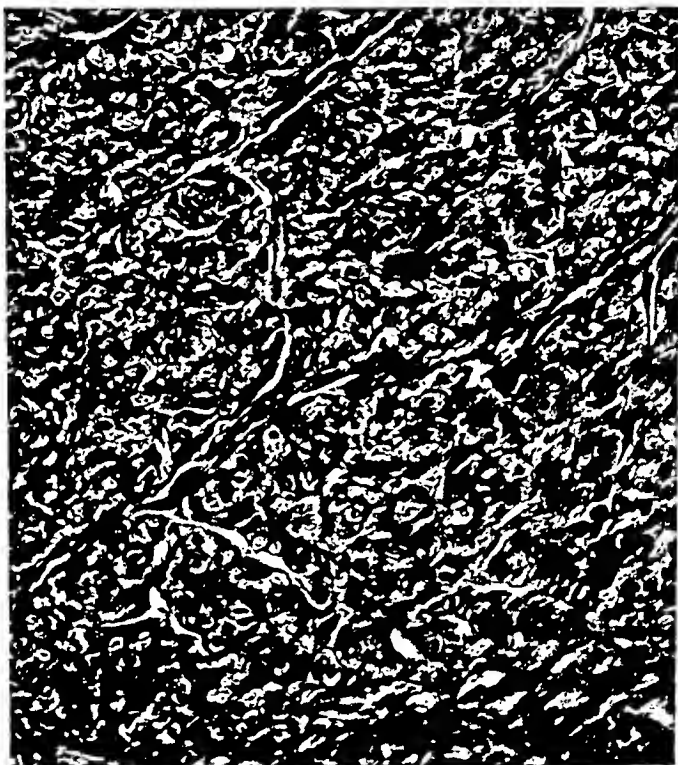


Fig. 2.—Section of uterine wall showing myometrial hyperplasia. Hematoxylin and eosin stain.  $\times 700$ .

From the above findings, i.e., the actual increase in the width of the muscle fibers, the absence of increase in the number of fibers per unit width of the uterine wall, and the failure to demonstrate an increase in fibrous tissue, it would seem that the increase in size of this group of uteri is due to the increase in size of the muscle fibers.

The one prominent symptom in these patients was abnormal uterine bleeding, occurring in the premenopausal decade. Shaw<sup>9</sup> spoke of a triad of bleeding, pain, and leucorrhea. In our observation pain has been absent and leucorrhea, when present, could be definitely traced to infection of the endocervical glands and was considered to be an incidental, rather than an integral, symptom.

As previously stated, the etiology is not altogether clear. Multiparity and age are the constant factors.

Infection, puerperal or postpuerperal, was believed to be an important factor by Blair-Bell<sup>4</sup> and a contributory factor by Shaw.<sup>9</sup> It is evident that most of the earlier writers thought of the condition as a chronic inflammatory process. There is nothing in the history or in the microscopic findings in our cases to point to infection or to chronic inflammation as etiologic factors.

Subinvolution has been given prominence as an etiologic factor by Serfert,<sup>11</sup> Shaw,<sup>9</sup> Novak<sup>10</sup> and others. The chief points in favor of subinvolution as a causative element are, first, the uniform multiparity of the patients, and second, the demonstrated fact that the uterine enlargement is due to an increase in the size of the muscle fibers. Novak points out that there is still a difference of opinion as to whether normal involution of the uterus is brought about by a great reduction in the cytoplasm of the individual cells, or by a diminution in the number of muscle cells. Subinvolution certainly cannot be ruled out on the basis of present knowledge.

Endocrine influences must also be taken into consideration as possible etiologic factors. The time of life at which this condition is found, and the hemorrhagic symptoms are all of suggestive importance. It seems fairly certain that approaching the actual development of the menopause there is a diminution in the secretion of progesterin resulting in a relative if not actual estrogen excess. As is known, estrogen causes an increase in the size of the uterus. It is possible that this may be an etiologic factor in the present cases. Confirmation will await estrogenic studies.

Although the myometrial hypertrophy is a constant finding in this group of uteri, it is evident that the actual mechanism of the uterine bleeding remains unexplained. It should also be emphasized that no constant histologic abnormalities could be demonstrated in the ovaries or endometrium.

In view of the present findings in this group of cases, it is apparent that the name "fibrosis uteri" is a misnomer, as evidence has been offered that there is no increase in the fibrous tissue but that the enlargement of the uterus is due to an actual increase in the size of the muscle fibers. For this reason it is suggested that the term "myometrial hypertrophy" be applied to these cases, at least until such time as the etiologic factor is definitely known.

### Summary

1. Ten cases of a distinct clinical entity consisting of patients suffering from uterine bleeding associated with a symmetrically enlarged, thick-walled uterus with little or no endometrial hyperplasia.

2. Evidence is presented that the increase in size of the uterus is due to a hypertrophy of the muscle fibers of the myometrium.

3. Various theories concerning the etiology of this condition are discussed. It is suggested that this condition may represent an estrogen effect.

4. The name "myometrial hypertrophy" is suggested for this condition in lieu of the previous terms: fibrosis uteri, chronic metritis, arteriosclerosis uteri, and metrorrhagia myopathica.

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## ORAL ADMINISTRATION OF PYRIDOXINE HYDROCHLORIDE IN THE TREATMENT OF NAUSEA AND VOMITING OF PREGNANCY\*

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THE successful control of nausea and vomiting of pregnancy which we previously obtained with the use of pyridoxine hydrochloride (B<sub>6</sub>) administered parenterally<sup>1</sup> led us to investigate the efficiency of the orally administered drug in the control of those symptoms. We report here the results in 78 cases.

In order to evaluate the results more accurately an attempt was made to grade the severity of nausea and vomiting present: morning nausea was considered 1+ (group 1); nausea extending throughout the day 2+ (group 2); nausea and occasional vomiting 3+ (group 3); nausea and vomiting of a degree prohibiting the retention of any fluids or solids 4+ (group 4). While most of the patients (52) fall into groups 1 and 2, the response of therapy was seemingly not dependent upon the severity of nausea and vomiting present, since several patients of group 4 responded as readily as those of group 1, while an occasional patient of group 1 failed to respond to therapy (Table I).

In all cases in group 1 an initial dose of 1 tablet (10 mg.) three times daily was used, the dosage being increased or decreased as necessary. Patients of group 2 received an initial dose of 2 tablets three times daily, while those of group 3 received 2 tablets three or four times daily. The patients classed in the 4+ group of necessity were first treated by hypodermically administered pyridoxine hydrochloride in doses of 100 mg. daily until vomiting was controlled and then maintained on oral dosage of 2 tablets four times daily. Some patients (especially groups 1 and 2) responded favorably within 24 to 48 hours and to as small a total dosage as 30 mg. In many cases 72 hours were required before symptoms were controlled. The largest total oral dosage given to any one patient was 2,500 mg. The largest combined oral and intramuscular total dosage given to any one patient was 2,280 mg. It may be noted that the large total dosage of oral drug in patients of groups 1 and 2 was not given through necessity, but because it was usually continued by the patient out of choice for a period of time after all symptoms had ceased.

\*Pyridoxine hydrochloride was supplied through the courtesy of the Medical Research Department of the Winthrop Chemical Company.



TABLE I—GROUP I  
(GRADED AS 1+, MORNING NAUSEA ONLY)

NO. OF PA- TIENT	DOSAGE (1 TABLET = 10 MG.)	TOTAL DOSAGE PRIOR TO RELIEF	TOTAL DOSAGE	RESULTS
1	30 mg. daily	60 mg.	420 mg.	Good
2	30 mg. daily	90 mg.	630 mg.	Good
3	30 mg. daily	60 mg.	420 mg.	Good
4	30 mg. daily	120 mg.	840 mg.	Good
5	30 mg. daily	30 mg.	420 mg.	Good
6	30 mg. daily	60 mg.	630 mg.	Good
7	30 mg. daily	120 mg.	840 mg.	Good
8	30 mg. daily	30 mg.	630 mg.	Good
9	30 mg. daily	30 mg.	420 mg.	Good
10	30 mg. daily	60 mg.	420 mg.	Good
11	30 mg. daily first 4 days; 60 mg. daily thereafter	600 mg.	1,840 mg.	Patient never completely relieved by B <sub>6</sub> therapy, though dosage was in- creased to 60 mg.; simple sedation alone did not suffice, but complete re- lief was obtained with B <sub>6</sub> and phenobarbital
12	30 mg. daily first 4 days; 60 mg. daily thereafter	90 mg.	630 mg.	Good
13	30 mg. daily first 4 days; 60 mg. daily thereafter	30 mg.	420 mg.	Good
14	30 mg. daily first 4 days; 60 mg. daily thereafter	120 mg.	630 mg.	Good
15	30 mg. daily first 4 days; 60 mg. daily thereafter	150 mg.	630 mg.	Good
16	30 mg. daily first 4 days; 60 mg. daily thereafter	180 mg.	630 mg.	Good
17	30 mg. daily first 4 days; 60 mg. daily thereafter	30 mg.	210 mg.	Good
18	30 mg. daily first 4 days; 60 mg. daily thereafter	60 mg.	420 mg.	Good
19	30 mg. daily first 4 days; 60 mg. daily thereafter	60 mg.	420 mg.	Good
20	30 mg. daily first 3 days; 60 mg. daily thereafter	930 mg.	1,600 mg.	See note for patient No. 11
21	30 mg. daily first 3 days; 60 mg. daily thereafter	30 mg.	210 mg.	Good
22	30 mg. daily first 3 days; 60 mg. daily thereafter	30 mg.	420 mg.	Good
23	30 mg. daily first 3 days; 60 mg. daily thereafter	120 mg.	630 mg.	Good
24	30 mg. daily first 3 days; 60 mg. daily thereafter	90 mg.	420 mg.	Good
25	30 mg. daily first 3 days; 60 mg. daily thereafter	60 mg.	420 mg.	Good
26	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	460 mg.	1,600 mg.	See note for patient No. 11
27	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	60 mg.	420 mg.	Good
28	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	90 mg.	420 mg.	Good
29	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	120 mg.	420 mg.	Good
30	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	180 mg.	630 mg.	Good
31	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	180 mg.	840 mg.	Good

TABLE I—CONT'D

NO. OF PA- TIENT	DOSAGE (1 TABLET = 10 MG.)	TOTAL DOSAGE PRIOR TO RELIEF	TOTAL DOSAGE	RESULTS
32	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	210 mg.	840 mg.	Good
33	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	60 mg.	420 mg.	Good
34	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	90 mg.	420 mg.	Good
35	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	60 mg.	420 mg.	Good
36	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	90 mg.	630 mg.	Good
37	30 mg. daily first 3 days; 60 mg. or 80 mg. daily thereafter	120 mg.	630 mg.	Good

The response to therapy is usually prompt. In group 1 the patients usually reported being symptom free within 48 hours, and a few were relieved within the first 24 hours; several required 72 hours or more. The most persistent case in group 1 (patient 11) did not become symptom free until the tenth day (Table I). This patient particularly interested us since she did not become completely relieved on either simple sedation (phenobarbital, gr.  $\frac{1}{2}$  t.i.d.) alone or on pyridoxine hydrochloride alone, though after 72 hours on combined therapy she was completely relieved. This was not an isolated observation since it was repeated in two other instances (patients 20 and 26). The results obtained in this group while good are not too impressive, since this type of patient frequently responds well to simple sedation. However, the rapidity of response to therapy is noteworthy. The rather

TABLE II—GROUP II.

(GRADED AS 2+, NAUSEA EXTENDING THROUGHOUT THE DAY)

NO. OF PATIENT	DOSAGE (1 TABLET = 10 MG.)	TOTAL DOSAGE PRIOR TO RELIEF	TOTAL DOSAGE	RESULTS
1	60 mg.	180 mg.	840 mg.	Good
2	60 mg.	180 mg.	840 mg.	Good
3	80 mg.	320 mg.	1,680 mg.	Good
4	60 mg.	120 mg.	840 mg.	Good
5	80 mg.	240 mg.	1,680 mg.	Good
6	80 mg.	240 mg.	1,680 mg.	Good
7	60 mg.	300 mg.	1,260 mg.	Good
8	60 mg.	120 mg.	840 mg.	Good
9	60 mg.	180 mg.	840 mg.	Good
10	60 mg.	180 mg.	840 mg.	Good
11	80 mg.	800 mg.	2,240 mg.	Continued to have occasional periods of nausea through- out four weeks of therapy
12	80 mg.	400 mg.	1,680 mg.	Good
13	60 mg.	240 mg.	840 mg.	Good
14	60 mg.	180 mg.	840 mg.	Good
15	60 mg.	180 mg.	420 mg.	Good
16	80 mg.	320 mg.	1,680 mg.	Good
17	60 mg.	360 mg.	840 mg.	Good
18	60 mg.	300 mg.	840 mg.	Good

large total dosages of B<sub>6</sub> given to these patients is attributable to their continuation of therapy long after cessation of symptoms. The excellent response of patients with more severe symptoms (groups 2, 3, 4) is more striking, and the results obtained in group 4 are particularly interesting. The daily dosage given in these groups is usually larger than in group 1, but the dosage effective for relief was in many instances relatively small (see Tables II, III, IV). The response of the group 3 and 4 patients is particularly gratifying since such patients who in the past were frequently hospitalized may now to a large degree be adequately and economically treated at home.

TABLE III—GROUP III  
(GRADED AS 3+, NAUSEA AND OCCASIONAL VOMITING)

NO. OF PATIENT	DOSAGE (1 TABLET = 10 MG.)	TOTAL DOSAGE PRIOR TO RELIEF	TOTAL DOSAGE	RESULTS
1	60 mg.	180 mg.	1,680 mg.	Good
2	80 mg.	800 mg.	2,240 mg.	Only partial relief; occasional nausea and vomiting
3	60 mg.	240 mg.	1,260 mg.	Good
4	60 mg.	240 mg.	1,680 mg.	Good
5	80 mg.	320 mg.	2,240 mg.	Good
6	80 mg.	400 mg.	2,240 mg.	Good
7	80 mg.	160 mg.	1,680 mg.	Good
8	60 mg.	180 mg.	1,260 mg.	Good
9	60 mg.	180 mg.	1,260 mg.	Good
10	80 mg.	240 mg.	2,240 mg.	Good
11	80 mg.	1,000 mg.	2,500 mg.	Relieved of vomiting; occasional attacks of nausea
12	80 mg.	160 mg.	1,120 mg.	Good
13	80 mg.	400 mg.	1,680 mg.	Good

There were no untoward reactions to the drug despite the fact that the total dosages were far in excess of those previously reported by ourselves<sup>1</sup> and by Willis et al.<sup>2</sup> No clear-cut quantitative relation between the oral and hyperdermatic dosages has been established, though we have observed that an oral dosage of approximately 3 to 5 times the hypodermatic dosage is required.

Occasionally a patient who became symptom free after a few days of therapy discontinued the medication and after a period of 2 to 5 days experienced a recurrence of symptoms. No patient who had a recurrence after previous complete cessation of symptoms failed to respond to therapy when it was resumed.

The administration of pyridoxine hydrochloride has certainly proved of value in this limited series of cases. While sedation was purposely restricted in this study, the importance of simple sedation and proper dietary supervision should continue to be stressed, and should be prescribed as usual with pyridoxine hydrochloride as a valuable adjunct in the therapy of nausea and vomiting of pregnancy. There are occasional "high strung" patients for whom pyridoxine hydrochloride plus sedation is of distinct value. The mechanism whereby pyridoxine hydrochloride relieves nausea and vomiting is unknown to us.

TABLE IV—GROUP IV

(GRADED AS 4+, NAUSEA AND VOMITING SUFFICIENTLY SEVERE TO PREVENT RETENTION OF ANY FOOD)

NO. OF PA- TIENT	DOSAGE	TOTAL DOSAGE PRIOR TO RELIEF (HYPO- DERM- ICALLY)	TOTAL DOSAGE H ORAL	RESULTS
1	100 mg. I.M. X 4; 60 mg. orally daily	600 mg.	<u>600</u> 1,260	Good
2	100 mg. I.M. X 6; 80 mg. orally daily	400 mg.	<u>600</u> 1,120	Good
3	100 mg. I.M. X 4; 80 mg. orally daily	300 mg.	<u>400</u> 1,680	Good
4	100 mg. I.M. X 6 daily; 80 mg. orally thereafter	500 mg.	<u>600</u> 1,680	Good
5	100 mg. I.M. X 4; 80 mg. daily	300 mg.	<u>400</u> 1,120	Good
6	100 mg. I.M. X 4; 80 mg. daily	400 mg.	<u>400</u> 1,680	Good
7	100 mg. I.M. X 4; 80 mg. daily	400 mg.	(400) (400) 160	Resumed vomiting after 2 days oral treatment; was treated with I.M. PH, in- fusions, sedation, etc.
8	100 mg. I.M. X 4; 80 mg. daily	300 mg.	<u>400</u> 560	Good
9	100 mg. I.M. X 8; 80 mg. daily	600 mg.	<u>800</u> 1,120	Good
10	100 mg. daily X 10; 80 mg. daily	300 mg.	(600) (400) 1,200	Vomited twice after cessa- tion of I.M. treatment; vomiting controlled by resuming I.M. treatment; received I.V. fluids, seda- tion, etc.

## Conclusions

1. Complete or considerable relief from nausea and vomiting of pregnancy was obtained in 68 patients who were treated with orally administered pyridoxine hydrochloride ( $B_6$ ) in dosages of 10 to 20 mg. three to four times daily, receiving total dosages of from 210 mg. to 2,500 mg.

Similar results were obtained in a group of 10 patients who received a combination of intramuscular and oral pyridoxine hydrochloride therapy; 8 patients obtained complete relief without recourse to supplementary therapy, and 2 patients required additional therapy.

2. Of 37 patients with nausea confined to the morning 34 were completely relieved, 3 partially relieved (Table 1). Of the 18 patients

with nausea extending throughout the day 17 were completely relieved, 1 partially relieved (Table II). Of the 13 patients with nausea and occasional vomiting 11 were completely relieved; 2 were relieved of vomiting but complained of occasional nausea (Table III). Ten patients with nausea and vomiting so severe as to prevent the retention of food were observed. Of these, 8 obtained complete relief with the combined use of orally and intramuscularly administered pyridoxine hydrochloride, and 2 required additional therapy (Table IV). This group showed the most noteworthy and impressive response, however they required closer supervision and greater individualization of therapy than the patients of the other groups.

3. No toxic manifestations were noted.

4. The use of pyridoxine hydrochloride has proved of value in this group of 78 patients, however the value of sedation and adequate dietary supervision should continue to command our attention, and should be utilized with pyridoxine hydrochloride as an important adjunct in the therapy of nausea and vomiting of pregnancy.

5. We believe that our results are sufficient to commend this drug for more extended trial and critical evaluation by others. A far larger series of patients must be carefully analyzed before final conclusions may be reached.

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1430 TULANE AVENUE

## THE SCALENUS ANTICUS SYNDROME AS A COMPLICATION AFTER GYNECOLOGIC OPERATIONS

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THE commoner complications following gynecological surgery relate, in the main, to disturbances of the gastroenteric, cardiorespiratory, and urinary systems. These complications, if anticipated, are readily detected, and when properly provided for, generally offer a favorable prognosis. Not always, however, is the patient so fortunate. There are other more infrequent and less clearly defined complications not so obviously associated with the operative procedure, whose symptoms may not become apparent for some time afterward. Furthermore, neglect may necessitate later surgery in a field remote from the original operative site. The authors wish to call attention to one of such post-operative complications, a neurocirculatory syndrome which may cause considerable difficulty with the neck, shoulder, and upper extremities. While knowledge of the symptomatology of neurocirculatory compression by lesions of the scalenus anticus muscle is not new,<sup>3-5</sup> the syndrome as an entity is usually encountered and treated by others than gynecologists.

The increasing frequency of detection and proof of compression of portions of the brachial plexus and subclavian artery by traumatic lesions of the scalenus anticus muscle indicates that this condition is one of the more prevalent causes of pain and unexplained vascular disturbance of the upper extremity. Similarity exists between the symptomatology of the scalenus anticus syndrome and that often associated with a clinical cervical rib.<sup>1, 2</sup> Furthermore, gross clinical findings in the two groups are similar save for the x-ray visualization of the extra rib. The symptoms are usually divided into: 1, nerve; and 2, vascular components. We feel that a third component comprised of sympathetic nervous system phenomena should be included. Combinations of these groups may be encountered. The usual symptom complex may be outlined as follows:

1. *Pain*.—Reference of the pain may be to any area supplied by the brachial plexus, but the ulnar distribution is usually the most affected, since the component roots, C-8 and T-1, pass from the median cord, which is anatomically in a position to be most affected. Pain, however, may be referred to the VII cervical spine, to the shoulder, to the elbow, and at times, to the lateral side of the neck, and to the scapular area.

2. *Subjective Sensory Disturbances*.—Numbness, paresthesia, and hypesthesia over the ulnar distribution may be frequent complaints.

3. *Objective Sensory Disturbances.*—Any one or all of the terminal branches of the brachial plexus may show reduction in function to the usual sensory tests. The objective findings are predominantly those of ulnar nerve area hypesthesia, and may be outlined over the small and ring fingers and over the lateral hand and wrist borders.

4. *Muscular Weakness and Atrophy.*—Typically weakness is both subjective and objective and usually involves the flexors of the fourth and fifth fingers, the small hand muscles, the abductors of the thumb and sometimes the flexors of the forearm. Atrophy is usually demonstrable in the muscles affected.

5. *Vascular Changes.*—The vascular changes are arterial in nature. Because the subclavian vein courses anterior to the scalenus anticus, it is usually little affected by traumatic changes of the muscle. The artery lying beneath the muscle is usually compressed by the lesion. There may be a concomitant decrease in the pulse volume and in blood pressure on the affected side. This may result in a decrease in surface temperature of the arm.

6. *Scalenus Anticus Muscle Tenderness.*—The symptom complex may, as a rule, be reproduced by pressure just above the origin of the scalenus anticus muscle. This reproduction of pain may be used for comparison and is of diagnostic value.

7. *Body Attitude.*—Patients suffering from this syndrome will often assume attitudes which give some measure of relief. These changes of position of the arm, head, or trunk all tend to relieve compression on the underlying structure by the scalenus anticus muscle. Patients tend to hold the affected arm across the upper abdomen when sitting, or to support it in the coat pocket, or with the opposite hand while walking. When lying down the arm is preferably elevated over the head, and the head tilted toward the affected side.

8. *Sympathetic Nervous System Changes.*—One occasionally sees a patient in whom typical attacks of migraine are precipitated by heavy lifting or by other strenuous work. In these persons a similar attack of headache may often be brought on by pressure on the scalenus anticus muscle. This is accomplished by unilateral pupillary dilatation and by increased perspiration over half of the face.

### Pathology

Briefly stated, the recently traumatized scalenus anticus muscle appears congested, hemorrhagic and swollen. Some of the muscle fibers may show evulsion. If the injury is severe, noticeable degeneration may occur. Inflammatory reaction may extend to adjacent structures, and with organization, fibrosis, and often times muscle shortening occurs. Tendinous bands may form and pass posteriorly and attach or be applied to the subclavian artery or brachial plexus, causing angulation and the characteristic symptom complex. The anatomic relationships are shown in Fig. 1.

### Etiology

Any incident which causes sharp, dorsal flexion of the lower cervical spine may lead to the onset of symptoms. Furthermore, acute postural change or any injury which causes tearing or undue stretching of the

scalenus anticus muscle with resultant hemorrhage into the muscle may serve as a background for a fibrosis or shortening of the muscle. Sharp inspiration usually accompanies this acute dorsal flexion and adds tension to an already stretched muscle. Common activities capable of inducing these acute postural changes are: diving, and throwing or catching some such object as a ball. The sudden dorsal flexion of an automobile driver's cervical spine, when the vehicle is violently struck from the rear, may be the etiologic agent. Faulty positioning of the patient on the operating table may also, we feel, be responsible for the underlying pathology.

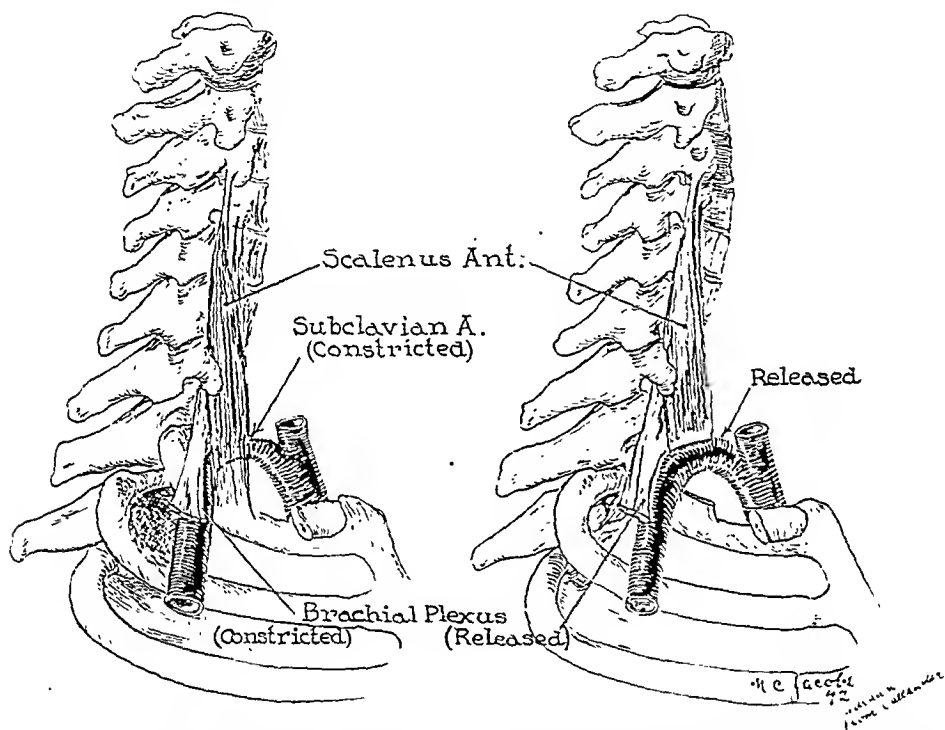


Fig. 1.—Right: Showing constriction of the subclavian artery and brachial plexus by the scalenus anticus muscle. Left: Showing release of constriction after sectioning the muscle.

On reviewing the case histories of patients presenting the characteristic features of the scalenus anticus syndrome in the neurosurgical clinic of the Strong Memorial Hospital, we were impressed with the time of onset of symptoms in certain patients. These patients had this in common: They first noted symptoms shortly subsequent to some prolonged gynecologic procedure. One of the authors (W. R.) has noted the syndrome following prostatic and orthopedic surgery. To satisfy themselves that faulty positioning of a patient on the operating table may be responsible for the syndrome, the authors themselves assumed the full Trendelenburg position. The immediate subjective symptom was a general discomfort which increased with the lapse of time. This discomfort seemed largely attributable to increased venous pressure in



the head and neck. The weight of the abdominal viscera against the diaphragm made respiration difficult. Hyperextension of the head in an attitude favorable to the duties of the anesthetist added to the discomfort. Definitely uncomfortable were the shoulders which were called upon to support a considerable portion of the body weight against even well-padded shoulder braces. Now, when an arm was extended in a position suited for intravenous fluid administration, the discomfort approached actual pain. It seemed improbable that even one in robust

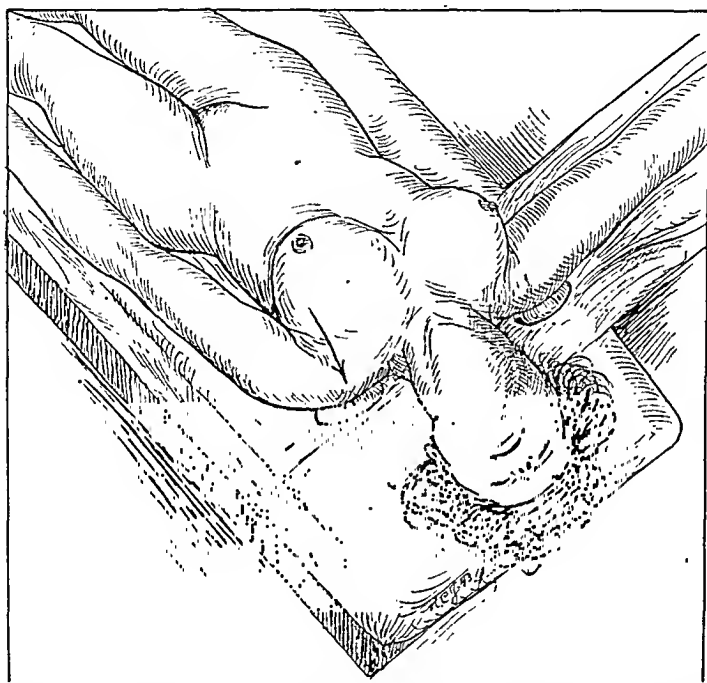


Fig. 2.—Patient in Trendelenburg position with right arm abducted for fluid administration. Note weight which left shoulder is called upon to bear under these circumstances. Hyperextension of the head adds to potential trauma to the scalenus anticus muscle.

health would long tolerate this unnatural position. When one now superimposes deep general anesthesia with resultant complete relaxation and further pressure of the body against the shoulder braces, no specially gifted imagination is required to visualize the potential damage to the scalenus anticus muscle and to the blood vessels and nerves in its environs. Under these conditions, the operating table may become a veritable rack. (Fig. 2.)

We present four typical cases of the syndrome in which the etiologic relationship to a gynecologic operation seems definitely established.

CASE 1.—(124578). Patient was a 49-year-old woman, having a myomatous uterus. The operation was a supravaginal hysterectomy, bilateral salpingectomy, and appendectomy. Ether anesthesia was used. The patient was in the Trendelenburg position some 50 minutes. On the third postoperative day, she noted numbness in the left small

and ring fingers. Along with this, there was a marked weakness of the left hand. Moderate discomfort of the lower cervical spine was noted. The symptoms persisted, and after two months were noted: Blood pressure in the right arm 166/96, in the left 158/90. The left radial pulse was weaker than the right. Hypesthesia was present along the ulnar nerve distribution of the left hand. The small muscles of the left hand were weak. Pressure over the scalenus anticus on the left side augmented the sensory disturbances. Rest and support of the left arm was advised. A second pillow under the head at night was also recommended. The symptoms and findings improved but still remained four months after operation.

CASE 2.—(88998). Patient was a 47-year-old woman with a diagnosis of myoma uteri. At operation supravaginal hysterectomy, right salpingo-oophorectomy, and appendectomy were performed. Ether anesthesia was used. The patient was in the Trendelenburg position about 40 minutes. About one month after operation she became aware of a dull aching pain over the left deltoid muscle. Stiffness of this arm interfered with motion. Shortly afterward she developed pain in the left side of the neck. There was slight tenderness over C5 and C6, where pressure caused pain in the upper arm. The reflexes in the left arm were more active than those in the right. Examination disclosed hypesthesia to pin prick over the ulnar distribution on the left side. The left pulse was weaker than the right. Blood pressure on the right was 124/80, on the left 116/76. Pressure over the scalenus reproduced the pain. Traction on the neck brought a degree of relief. The patient was more comfortable when the left arm was abducted and externally rotated. The patient improved with rest and after four months was symptom free.

CASE 3.—(156323). Patient was a 54-year-old woman with a diagnosis of relaxed pelvic floor with cystocele and rectocele, and salpingitis, right. At operation, repair of the cystocele and rectocele, right salpingo-oophorectomy, and appendectomy were performed. Ether anesthesia was used. The patient was in the Trendelenburg position about 50 minutes. Some two months after operation, she first noted paresthesia along the course of the left ulnar nerve. This later spread to the left shoulder and arm. The pain was aggravated by motion of the arm and was not relieved by heat and simple physiotherapy over a three-month period. Injection with novocain brought some relief. Prolonged physiotherapy resulted in benefit, but motion of the arm remained limited for six months. Pressure over the scalenus anticus muscle still reproduced the pain. At operation, the characteristic chronic lesion of the muscle was noted. Resection of this muscle resulted in prompt relief of symptoms.

CASE 4.—(61807). The patient was a 35-year-old woman having a relaxed pelvic floor with cystocele, rectocele, and chronic cervicitis. The operations performed were: eurettag, eauterization of the cervix, radical repair of the cystocele and rectocele, and perineorrhaphy. During the course of the operation, under ether, the patient was given 1,000 c.c. of 5 per cent glucose into the left cubital vein. On getting up two weeks following operation, the patient experienced pain in the right scapular region. This pain was aggravated by coughing. Two weeks later the pain radiated down the right arm. The fingers on this

side felt numb. Hypesthesia was noted over the entire hand. The blood pressure on the right was 110/60, and on the left was 118/76 at this time. Pressure over the right anterior scalene reproduced her discomfort. Local physiotherapy was of no benefit. Four months after the first operation, the right anterior scalene was sectioned. Local pathological changes were typical of the lesion. Full recovery was prompt.

### Comment

As one might expect, the following conditions entered into the differential diagnosis and should always be considered when this syndrome is suspected:

- a. cervical rib.
- b. brachial plexus root evulsion or brachial plexus tears.
- c. peripheral neuritis of all types of etiology.
- d. bone and joint pathology about the shoulder girdle joint.
- e. bursitis of shoulder joint.
- f. tendon injury of the shoulder.
- g. spine fractures (cervical).
- h. myalgia.

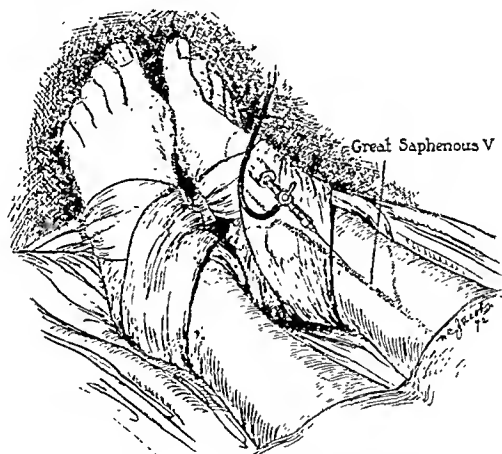


Fig. 3.—Patient partially suspended by straps applied to ankles and feet. This removes some of the weight from the shoulder braces. Vein available for fluid administration.

Protracted symptomatology, despite palliative treatment, was a feature in each of the cases reviewed. These cases, we feel, presented adequate basis for the diagnosis as given, although in only two cases was the diagnosis confirmed at operation. It is the opinion of the authors that faulty positioning of the patient on the operating table was the etiologic factor. Placing the patient in the severe Trendelenburg position, while it greatly facilitates pelvic surgery by invoking the aid of gravity in helping to remove the intestines from the immediate operative area, nevertheless, may be a definite cause of danger. Before subjecting the patient to such a long, unphysiological position, the surgeon should well consider the advantages he hopes to gain against possible dangers which are doubtless more real than has often heretofore been regarded.

## Prophylaxis

When one considers the underlying etiology of this syndrome, preventive methods immediately come to mind. If an extreme Trendelenburg position of the patient is actually required, the patient should be maintained in this position as briefly as possible. The shoulder braces should be well padded. The anesthetist should exercise special caution in not causing needless hyperextension of the head. By placing appropriate, well-padded straps about the ankles and feet (Fig. 3), a method of applying traction to the lower extremities is available whereby one is enabled with safety to suspend the patient partially by the lower extremities. This relieves the shoulders of the need of supporting a great share of the body's weight. Should there be need of administration of fluid, care should be exercised in the abduction of the arm. Furthermore, as is shown in Fig. 3, an intravenous needle can under these circumstances readily be inserted into the great saphenous vein just above the internal malleolus, should the need for parenteral fluids arise during the course of the operation. This obviates the use of the practice of abducting the arm for this purpose, a procedure that throws an additional critical burden on the shoulder on the opposite side.

## Summary

The syndrome of neurocirculatory compression by lesions of the scalenus anticus muscle is reviewed, and four cases illustrating this syndrome are presented.

1. This syndrome may result from the faulty positioning of the patient on the operating table. Injury to the scalenus anticus muscle may be caused by shoulder braces when the patient is maintained in Trendelenburg position, especially when one arm is abducted for intravenous fluid administration and when the head is hyperextended during the administration of the anesthetic.

2. Prophylactic measures relate to protection of the scalenus muscle during the operation.

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# PERIPHERAL CIRCULATORY COLLAPSE IN TOXEMIA OF PREGNANCY

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## Introduction

THE subject of peripheral circulatory collapse or shock in toxemia of pregnancy had not received much emphasis until recent years. Dexter and Weiss,<sup>1</sup> in their comprehensive work on the subject of toxemia of pregnancy, were the first to stress its practical importance. A review of the obstetric texts prior to that time shows that the severe hypertension, the convulsions and the lack of diuresis were considered the most serious factors in the disease. In addition, primary central cardiac failure was regarded as an important cause of death in severe cases. Discussions of therapy<sup>4, 5</sup> were mainly concerned with control of convulsions, lowering the blood pressure, prevention of cardiac failure and specific measures to promote diuresis.

Dexter and Weiss<sup>1</sup> introduced new conceptions of the pathologic physiology of the disease. They argued that the cardiac failure was largely due to water retention and that primary central congestive cardiac failure is not common in an uncomplicated case of toxemia of pregnancy. They stated that peripheral circulatory collapse is the most important complication of toxemia of pregnancy and may have considerable influence in determining the prognosis of a given case. They recommended the use of blood transfusion or concentrated protein solutions to combat this collapse.

Plass<sup>2</sup> in a summary of his experience with toxemia of pregnancy expressed the same attitude with regard to the frequency of circulatory collapse in that disease. He states, "Patients with late pregnancy toxemias are prone to circulatory collapse in the presence of even small post-partum blood loss." Plass<sup>2</sup> further states that, "The susceptibility of severely toxemic and eclamptic patients to shock is not yet fully appreciated despite its obvious importance."

Very recently, Dexter<sup>3</sup> and his associates have made another excellent contribution to the understanding of toxemia of pregnancy and of the importance of circulatory collapse in that disease. They now state, "Although an extreme hypertension in eclampsia is of danger to the patient, it has been our experience that the earliest sign of impending disaster is almost always an insidious, progressive fall in arterial blood pressure terminating in shock and death." These authors believe that part of this drop is due to the "disintegration of the body as a result of the disease." They repeat the opinions<sup>1</sup> given in 1941 that transfusion of blood or administration of concentrated protein solutions is the most important measure for checking the progress of circulatory collapse. They further warn that the prognosis will be most grave if

this therapy is not given before frank shock, with low blood pressure, pulmonary congestion, gasping respirations, cyanosis, coma, and cold clammy extremities, sets in, because irreversible changes have occurred by that time.

### Discussion of Cases

This report is primarily concerned with nine patients who illustrate well the importance of peripheral circulatory collapse in severe toxemia of pregnancy. Only the data directly concerning the circulatory collapse are presented. All the patients had severe toxemia of pregnancy with 4-plus albuminuria. They represent all grades of circulatory collapse, from a slight elevation of the pulse and fall in blood pressure, to frank shock.

The definition of peripheral circulatory collapse or shock as applied to these cases is the generally accepted one for the other fields of medicine and is the same as that of Dexter<sup>1, 3</sup> and his associates. In early stages the diagnosis is difficult because often only slight changes in blood pressure and pulse are evident. To establish its presence the physician must observe the patient frequently for slight elevation of the pulse rate and decrease in its volume which may precede any drop in blood pressure. Such attention was given the patients presented in this report.

The treatment of these patients was very conservative and included the usual measures for toxemia. All received whole blood plasma intravenously when any signs of circulatory collapse appeared. The collapse developed so suddenly in some patients that they received plasma only after signs of frank shock were present. In others, the process was more insidious; these patients received plasma after slight pulse and blood pressure changes.

Continued improvement was always accompanied by diuresis. It is not certain whether the diuresis was in part the result of the plasma therapy. However, this remains a distinct possibility and deserves further study.

Other factors which might have influenced the development of collapse in any case are specifically mentioned in the summary of that case. No patient had excessive blood loss. No severe infections occurred.

### Abbreviated Case Summaries

CASE 1 (A69140—Duke Hospital).—Forty-two-year-old, colored, married; para vii-i-vi; admitted Sept. 9, 1941, because of severe toxemia; four convulsions before admission. C.D.C. Oct. 15, 1941. Admission blood pressure 210/110; after five hours spontaneous delivery of still-born (2,000 Gm.); blood pressure dropped immediately to 100/80. Pulse very weak and fast. Other signs of shock present. Five hundred c.c. of plasma administered. Blood pressure 120/100. Within one hour blood pressure 100/60; pulse very faint. Five hundred c.c. of plasma administered. Blood pressure 150/100; pulse improved. The remaining hospital course uneventful.

CASE 2 (A70959—Duke Hospital).—Twenty-three-year-old, colored, married, para 0; admitted Sept. 21, 1941, because of severe toxemia. C.D.C. Nov. 27, 1941. Admission blood pressure 180/110. After five days of conservative management, blood pressure 220/150. Artificial rupture of membranes, spontaneous delivery of stillborn (1,300 grams). Ten hours after delivery blood pressure suddenly dropped to 100/40; pulse weak and rapid. Eight hundred c.c. plasma administered. Blood pressure up to 140/100; pulse improving. Remaining hospital course uneventful.

CASE 3 (A73484—Duke Hospital).—Seventeen-year-old, white, married, para 0; admitted Nov. 7, 1941, because of severe toxemia. C.D.C. Oct. 15, 1941. Admission blood pressure 164/110. After four days of conservative management, blood pressure 200/130. Artificial rupture of membranes. First twin delivered by low forceps and second by very easy version and extraction, both infants viable (2,000 and 1,900 grams respectively). After fifteen minutes blood pressure dropped to 110/76. Pulse very rapid and weak. Eight hundred c.c. plasma administered. Blood pressure 150/100; pulse improved. Remaining hospital course uneventful.

CASE 4 (A74343—Duke Hospital).—Twenty-year-old, colored, married, para ii-o-ii. Admitted Nov. 17, 1941, because of severe toxemia. C.D.C. Jan. 15, 1942. Admission blood pressure 210/150. After four days of conservative management patient went into labor. During labor blood pressure 300/170. Patient became very irrational. Spontaneous delivery stillborn (2,400 grams). Blood pressure then dropped steadily and rapidly. Signs of severe circulatory collapse developed in spite of treatment. Fifteen hundred c.c. of plasma were administered. Patient expired in deep shock three and one-half hours after delivery. This patient had no convulsions. Autopsy revealed very extensive hemorrhagic necrosis of the liver and kidney.

CASE 5 (74016—Duke Hospital).—Thirty-two-year-old, white, married, para 0; admitted Nov. 30, 1941, because of severe toxemia. C.D.C. Jan. 4, 1942. Admission blood pressure 200/130. After four days of conservative therapy, blood pressure 210/150; spontaneous onset of labor. Low forceps delivery of stillborn (2,050 grams). One hour later blood pressure 140/90 and pulse very rapid. Five hundred c.c. plasma administered; blood pressure up to 160/110; pulse improved. Remaining hospital course uneventful.

CASE 6 (A76503—Duke Hospital).—Twenty-year-old, white, married, para 0; admitted Dec. 29, 1941, because of severe toxemia. Admission blood pressure 200/130. After three days of conservative therapy, blood pressure 190/130. Medical induction of labor; low forceps delivery; viable infant (3,325 grams). Blood pressure dropped immediately to 130/90 and pulse became more rapid. One thousand c.c. of 10 per cent glucose in distilled water administered without improvement. In half hour blood pressure 80/50 and pulse weaker. Five hundred c.c. of plasma administered. Blood pressure 140/90; pulse improved. Remaining hospital course uneventful.

CASE 7 (A65251—Duke Hospital).—See attached graphic chart. The accompanying graph (Fig. 1) shows patient's course for thirty-seven

hours after admission. This case illustrated the use of plasma repeatedly in the early stage of circulatory collapse before and after delivery.

CASE 8 (17665—Station Hospital, Camp Rucker, Ala.).—Twenty-one-year-old, white, married, para 0; admitted April 20, 1943, because of severe toxemia. C.D.C. May 6, 1943. Admission blood pressure 160/100. After twelve days of conservative therapy, blood pressure 170/116. Artificial rupture of membranes; progress of labor was slow. Pulse advanced from 96 to 150 in twenty-four hours; blood pressure 180/120; 250 c.c. of plasma administered. Low forceps delivery of viable infant (3,000 grams). Four hours after delivery pulse 120 and weak; blood pressure 160/80; 250 c.c. plasma administered; pulse improved. Remaining hospital course uneventful.

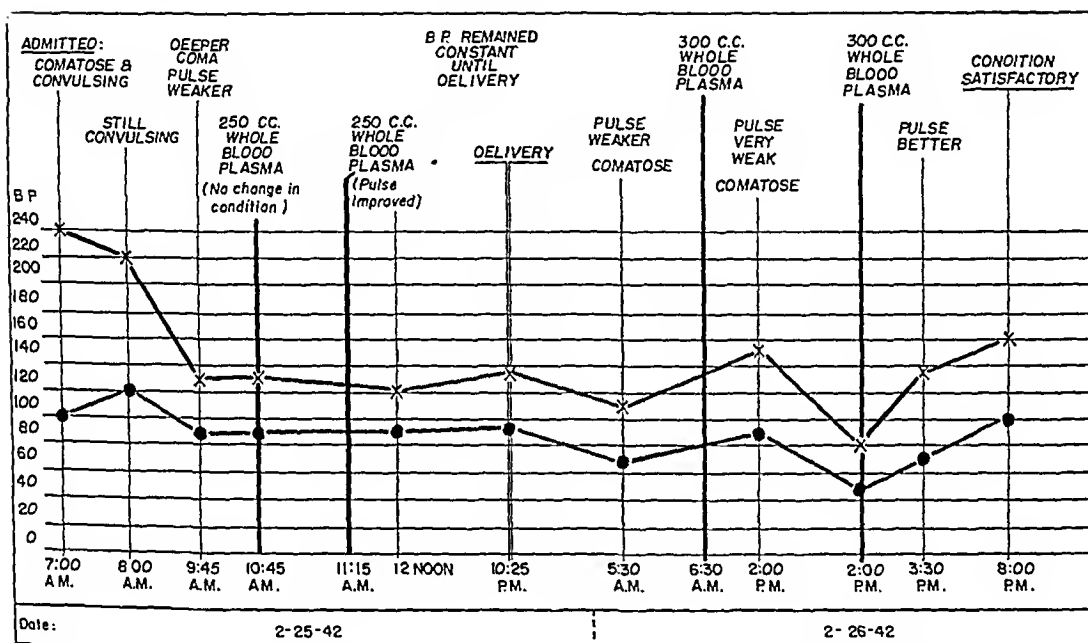


Fig. 1.—Case 7 (A65251). W.M.F., Para 0-0-0, aged 17 years. No convulsions until being admitted. C.D.C. March 8, 1942. Labor 8 hours. Small episiotomy. Spontaneous delivery. Stillborn infant, weight 3,470 Gm.

CASE 9 (18882—Station Hospital, Camp Rucker, Ala.).—Twenty-year-old, white, married, para 0; admitted May 14, 1943, because of severe toxemia and premature rupture of membranes. C.D.C. May 12, 1943. Admission blood pressure 170/130. Labor progressed slowly. Twenty-four hours after admission low forceps delivery of viable infant (2,500 grams). Blood pressure 140/90 and pulse 140; 500 c.c. of plasma administered. Three hours after delivery patient showed symptoms and signs of impending convulsions; blood pressure up to 170/100 and pulse 130. After sedation blood pressure dropped to 140/90 and pulse up to 148 and very weak. Five hundred c.c. of plasma administered with slight improvement in pulse. Eleven hours after delivery blood pressure 110/90 and pulse much weaker. Five hundred c.c. of plasma administered. Blood pressure up to 160/120 and pulse improved. Thirty-six hours after delivery pulse weaker. Five hundred c.c. of plasma administered; pulse improved. Remaining hospital course uneventful.



### Summary

1. The current literature on circulatory collapse in toxemia of pregnancy has been reviewed.

2. Nine patients with varying degrees of circulatory collapse have been discussed.

3. Whole blood plasma apparently is effective therapy for peripheral circulatory collapse in toxemia of pregnancy if used in the early stages.

The author wishes to express appreciation for the criticism of Dr. Bayard Carter, Durham, N. C., in the preparation of this paper.

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## RATE OF TRANSPORT OF SPERMIA IN HUMAN UTERUS AND TUBES\*

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AS EARLY as 1853, Leuckhart and Bischoff attempted to determine the rate of locomotion of spermia in the female genital tract. They recovered several spermia from a guinea pig's ovarian bursa within 15 minutes following coitus. Whitney (1927), recovered them from the bursa of the female dog within 18 minutes; Lewis and Wright, (1935), within 15 minutes in the ewe.

Previous investigators found more protracted periods. Quinlan and Marl (1931), Green and Winters (1935), found spermia in the ewe bursa only after 5 hours. Pincus (1930), did not find them in the rabbit bursa until 3 hours had elapsed.

### Method and Manipulative Technique

From complete abdominal hysterectomies at Barnes Hospital gynecology department, St. Louis, six uteri and tubes were made available for these determinations. The experiments were started one to three hours following excision. The uterus, in each instance, was warmed to body temperature in a 37° C., incubator. In the first three specimens studied the uterine artery was perfused with 37° C., physiological saline solution during the determinations. During each experiment the uterus and tubes were wrapped in warm saline compresses. The angles were adjusted to simulate the normal in vivo position of the uterus and adnexa. A 2 c.c. pool of sperm  $\frac{1}{2}$  to 3 hours post-ejaculatory was placed in an appropriate receptacle at the cervical end of the excised uterus. The sperm was collected from the donor into a glass vial and was tested for viability (Brown and Gamble, 1940, 1941). At ten-minute intervals for the first half hour and every five minutes thereafter, the fimbriated end of the Fallopian tube was immersed two or three times in a drop of physiological saline solution previously placed on a micro-slide. The drop was then covered with a cover slip and examined for living spermia. Three excised Fallopian tubes were similarly placed in contact with a measured quantity of sperm (0.3 c.c.) and the fimbriated ends examined every 3 to 5 minutes.

Six separate experiments were attempted; three of the six uteri gave satisfactory results. The case histories are as follows:

CASE 1.—A 36-year-old white married female; gravida iii, para iii. Diagnosis: multiple myomatous uterus, ovarian cyst. Operation: complete abdominal hysterectomy and unilateral salpingo-oophorectomy on one side and salpingectomy on the other. The excised uterus was 7 cm.

\*Invaluable suggestions were made by Dr. Clarence J. Gamble of the National Committee on Maternal Health and also by Dr. T. K. Brown, St. Louis Maternity Hospital, Barnes Hospital, and Washington University Medical School.

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long; the uterine canal was 6.2 cm. in length to the fundus. The Fallopian tube was 11.3 cm. long. Allowing 2 cm. for the uterine horn, the spermia traveled approximately 19.5 cm. to the fimbria.\* The uterus was excised at 3:45 P.M., and was perfused with 37° to 38° C., normal saline solution at 4:50 P.M. The cervical canal was probed for patency. The cervix was placed in a pool of sperm from donor A at 5:21, and the spermia were observed in the drop at 6:29. The time required for the spermia to migrate through the uterus and tube was 68 minutes. The excised tube was 5.5 cm. long and the migratory period was 17 minutes (5:22 to 5:39).

CASE 2.—A 47-year-old white married female; gravida 0, para 0. Diagnosis: sterility, multiple myomatous uterus, hydrosalpinx. Operation: complete abdominal hysterectomy, bilateral salpingectomy, ovarian cyst incised. Experiment started at 6:26 P.M. after perfusion and wrapping with compresses. No spermia present at ostia by 9:00 P.M. (2 hours, 34 minutes).

CASE 3.—A 54-year-old white married female; gravida 0, para 0. Diagnosis: sterility, multiple myomatous uterus, pelvic adhesions, and moderate hydrosalpinx. Patient had history of Neisserian salpingitis prior to marriage. Operation: complete abdominal hysterectomy, unilateral salpingo-oophorectomy. Pool of sperm from donor A placed at cervix of prepared uterus at 11:42 A.M. no spermia observed at 4:00 P.M. (4 hours and 18 minutes).

CASE 4.—A 43-year-old white married female; gravida i, para i. Diagnosis: multiple myomatous uterus and multiple cystic ovary. Operation: complete abdominal hysterectomy, unilateral salpingo-oophorectomy and salpingectomy on opposite side with incision of ovarian cysts on that side. Uterus was 7.4 cm. long; the uterine cavity, 6.4 cm. to fundus. The Fallopian tube was 10.5 cm. long. Spermia traveled approximately 18.9 cm. to fimbria. The uterus was excised at 11:00 A.M., was not perfused but warmed in incubator at body temperature and wrapped in compresses at 12:30 P.M. The spermia from donor B were recovered from the fimbriated end in 71 minutes (12:39 to 1:50). The excised tube measured 5.5 cm.; spermia were recovered in 23 minutes (12:40 to 1:03).

CASE 5.—A 34-year-old colored married female; gravida iii, para ii. Diagnosis: myomatous uterus, cystic ovaries. Operation: complete abdominal hysterectomy, unilateral salpingo-oophorectomy and salpingectomy on opposite side. The uterus was 8 cm. long, the uterine canal was 6.0 cm. deep. The attached tube was 9.8 cm. long. Spermia from donor C traveled approximately 18.3 cm. to ostia. The uterine horn was lengthened to 2.5 cm. due to the myoma impinging on the fundus portion of the uterine canal. The uterus had been excised 1 hour, 22 minutes and had been in the incubator 45 minutes of this time before sperm from donor B was placed at cervix. The transport time was 68 minutes (4:03 to 5:11). The excised tube was 5 cm. long and spermia were recovered from its fimbria in 23 minutes (4:23 to 4:46).

CASE 6.—A 37-year-old white married female; gravida i, para i. The patient had had "pelvic inflammatory disease" of unknown etiology since childbirth. Diagnosis: Pelvic adhesions, myomatous uterus. Spermia from donor B could not be recovered in 4½ hours.

\*The uterine horn, a portion traversed by the spermia, was not measured, accounts for the apparent 2.0 cm. discrepancy. The mucosal surfaces add an unknown quantity to the distance the uterine and tube traversed.

## Results and Determinations

The results of these experiments as summarized in Table I, indicate that the average rate of transport of spermia through the patent canal of the three excised human uteri and Fallopian tubes was 69 minutes. The average distance traversed was approximately 18.9 cm., 8.4 cm. of which was from the external cervical canal to the junction of the uterine horn and the Fallopian tube, and the remaining 10.5 cm. constituted the tube to the ostium.\* By interpolation and by assuming that the rate throughout the length of the tube was constant the average time to traverse the entire tube was 41.7 minutes. This leaves 27.3 minutes for the uterine cavity. The average distance per minute throughout the uterus and tube was 2.73 mm.; in the uterus alone it was 3.1 mm. and in the Fallopian tube, 2.5 mm. per minute.

## Discussion

*Rate of Transport Variable.*—Heretofore the speed of and time for transport of spermia in the human female reproductive system was unknown. Earlier experiments offered no direct application. Furthermore, the varying distance to be traversed to the fimbria among and within species made identical times of transport to the bursa unlikely. Also the morphology of the copulated genitalia in several species (including dog and guinea pig), permits the deposition of semen within the uterus, with resulting shorter distance to the fimbria or bursa. It is also very likely that the vitality and morphology of spermia affect their rate in utero. This may well account for the discrepancy in data of previous investigators. It would appear after consideration of the above influencing factors that identical rates of transport and locomotion of spermia among and within species are coincidental.

*In Vivo and in Vitro Rates Compared.*—Although the in vitro rate for mammalian spermia has varied with the experimenter the average is about 3 mm. per minute. Parker (1931) determined 3.6 mm. Lloyd, Jones, and Hays found the same rate previously (1918). Hansen (1881) found 1.0 mm. The in vitro determinations of Phillips (1935) for ram spermia was 4.6 mm. per minute. He devised a glass tube which approximated the length of the uterus and tubes of the ewe and "tapped" the media at intervals to determine the rate of transport.

TABLE I. SPERMIA TRANSPORT

CASE NO.	DISTANCE TRAVERSED IN CM.			TOTAL TIME REQUIRED IN MINUTES			DISTANCE PER MINUTE IN MM.		
	COM- BINED	UTERUS	TUBES	COM- BINED	UTERUS	TUBES	COM- BINED	UTERUS	TUBES
1	19.5	8.2	11.3	68	33	35	2.9	2.5	3.2
3	18.9	8.4	10.5	71	27	44	2.6	3.1	2.4
5	18.3	8.5	9.8	68	22	46	2.7	3.4	2.2
AVERAGE	18.9	8.4	10.5	69	27.3	41.7	2.73	3.1	2.5

\*Spermia were undoubtedly "sponged" from the ostium rather than the terminations of the fimbria by the method used.

Under conditions approximating the *in vivo*, spermatozoa transport times through excised human uterus and tube, collectively and separately, were determined. A portion of the tube only was excised and tested, but the transport time of this section was interpolated in terms of the full length tube. The 17 per cent difference between transport times in the tube and uterus may not be significant. Variable factors may conceivably produce a much greater difference.

Disregarding other factors this same rate would require 83 minutes *in vivo*. These figures compare favorably with 2.7 mm. per minute and a transport time of 69 minutes. (See Table I.)

*Corrected Factors Which May Affect the Time.*—The experiments were carried out at body temperatures to simulate *in vivo* conditions. The locomotion rate was decreased with both markedly increased and decreased temperatures. Furthermore the sperm was collected with all essential precautions (See Brown and Gamble 1940, 1941). The uterine and Fallopian cavities were left *per se*; thereby providing the normal environment. The uterine cavity was adjusted to *in vivo* position. A retrograde current was provided by the normal flagellating epithelial cilia.

Such a current, whether natural or induced, usually orients spermia mechanically (Adolphi 1905, 1906). Human spermia were observed to be no exception. An adequate current forced and maintained the flagellating tail downstream; thereby necessitating retrograde locomotion.\*

*Time to Reach the Ovum (Interpolated).*—There is evidence that fertilization does not occur with the first spermium arrival but only after many are adjacent to the ovum (Hammond, 1934). The transport time of spermia to this region is approximately 65 minutes. They are in abundance in this region in 70 to 75 minutes and may be recovered from the ostium for 2 hours at least after the cervix has been removed from the sperm pool.† Therefore, it would appear that contact of ovum and fertilizing spermium in a patent human genital tract is most likely to occur from 65 to 75 minutes after the sperm is deposited in the fornices. Actual fertilization occurs several hours later (Pineus, 1930).

### Summary

1. The average time (three determinations) for human spermia to traverse the excised human uterus and tubes at near *in vivo* condition was 69 minutes. Twenty-seven minutes of this occurred in the uterus, 42 in the Fallopian tubes (interpolation).

2. The average distance traversed was 189 mm.; 84 in the uterus, 105 in the tube. The average distance in mm. per minute was 2.7.

3. The average time for ejaculated spermia to reach the ovum in women is 65 to 75 minutes (interpolated).

\*It is apparent that the retrograde current may slow the rate of the individual spermium, but assures a much greater number of spermia to a given destination.

†The senile spermia (Brown and Gamble, 1940, 1941, 1943), which fall by the wayside, would have been unimportant to fertilization had they ultimately arrived, as the fertilization power wanes before cessation of locomotion and death (Hammond, 1930)—thus a spermium climacterium.

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## ACARDIUS AMORPHUS

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SINCE the report of the first case by Benedetti<sup>1</sup> in 1533 to the present, only sixty-three cases of acardius amorphus have been reported in the medical literature. This rarer type of monster has also been described under the names fetus amorphus and holoacardius amorphus. The term fetus amorphus was initially used by Gurlt<sup>2</sup> in 1832 and this type of monster was first fully described by Geoffrey St. Hilaire<sup>3</sup> in 1838. Either of the terms acardius amorphus or holoacardius amorphus is to be preferred, since this terminology points to the classification of these fetal abnormalities, in that the heart is absent; whereas the term fetus amorphus simply denotes a fetal abnormality with an amorphic shape. The term holoacardius is used to differentiate the anomaly in which the heart is entirely absent, from the type known as hemiacardius, that possesses a rudimentary heart.

"An acardius is a one-egg twin with an absent, or rudimentary, non-functioning heart, whose circulation is mainly or wholly carried on by the heart of its healthy co-twin. Moreover, in part of the vascular system of the acardius, the blood flows in a direction which is contrary to normal."<sup>4</sup> Acardii also occur in triplet, quadruplet pregnancies, and in animals. Simonds and Gowen<sup>6</sup> list twelve occurrences in cattle, three in sheep, and one in a bird.

The classification of acardii is somewhat in dispute in that Stander,<sup>5</sup> DeLec,<sup>7</sup> and others<sup>4, 8</sup> claim they are divided into two main groups: the hemiacardii and the holoacardii. The holoacardii are then separated into three subgroups: the acephali, acormi, and amorphi. The other classification is that given by Simonds and Gowen<sup>6</sup> who divide the acardiac group of monsters into five subgroups:

1. Amorphus or anideus, has not acquired the external form of a fetus and appears as an irregular skin-covered mass.

2. Mylacephalus, an amorphus mass with suggestions of one or more limbs.

3. Acormus, development of head only. Umbilical cord may be attached to the cervical region.

4. Acephalus, trunk and limbs more or less well developed but head entirely absent.

5. Anceps or paracephalus, head very imperfectly developed, trunk and limbs fairly well developed.

The specimen to be described herein, in all probability, would fall into the group of mylacephalus of Simonds and Gowen<sup>6</sup> but the simpler classification preferred by the majority will be used.

The amorphi have little semblance of human form. They are an irregularly-shaped mass, with or without appendages covered by skin. Bone is usually found within the mass. Various other organs may also be found, the most frequent being striated muscle, intestine, nerve, renal, hepatic, and lymph tissue.

Acardii amorphi have been described as being of various shapes as: egg-shaped, reniform, globose, triangular, oval, etc., the length varying

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from 4.5 cm. to 40 cm., the majority being from 5 to 15 cm.; and the weights ranging from 170 grams to 2,020 grams.

The circulation of blood in an acardius is interesting. According to Guttmacher<sup>4</sup> "the driving force is the heart of the normal twin. The blood travels from the heart of the normal twin via its umbilical arteries and their placental anastomoses, directly into the umbilical arteries of the acardius. Since the umbilical arteries of the acardius possess no positive pressure, which in embryos with a normal heart is generated by fetal cardiac pulsations, the blood instead of flowing away from the monster flows toward it. After coursing through the monster it then flows to the placenta through the monster's umbilical vein. The blood supplied to the acardius is relatively low in oxygen, since it comes direct from the umbilical arteries of the co-twin just after having coursed through its body, and is shunted to the acardius before being oxygenated via the placental blood spaces."

Das<sup>9</sup> reviews forty-five cases of acardiac monsters (including acephalus, acornus and amorphus) and contrary to earlier belief that acardiac monsters were rarely born in first labors, in the ten cases in which parity was given, five were in primiparas. In the review of fifty-six cases (including true acardius amorphus and mylacephalus) Simonds and Gowen<sup>6</sup> limit their discussion to the monstrosity alone and present no clinical data. The cases of Beerens<sup>10</sup> and Schultze<sup>11</sup> were both in primigravidas, whereas those of Van Tongeren,<sup>12</sup> Ruge,<sup>13</sup> and Risel<sup>18</sup> were multiparas. A previous history of multiple pregnancy in the same patient is rare.

The duration of pregnancy in six of eleven cases was full term.<sup>9</sup> Hydramnios is usually present. In twelve of fourteen cases<sup>9, 10, 12, 19</sup> the healthy twin was born first. In the other reports no mention is made of the order of birth. The presentation was noted in six cases:<sup>9</sup> two were footling, two breech, and two in which the cephalic end presented. According to Halban and Seitz<sup>16</sup> an acardius usually presents by the breech and is delivered within twelve hours after the normal twin.

As the abnormality is one arising from uni-ovular and monochorionic twins the sex apparently should be the same in both the normal child and the acardius. This has generally been found true in all sixty-three cases with the exception of two doubtful incidents: the one case noted by Das<sup>9</sup> and that recently reported by Buxbaum and Wachsmann.<sup>15</sup>

"Statements concerning the incidence of acardii are few," Guttmacher claims. "Among 475 plural pregnancies Strassman<sup>17</sup> had two acardii. In 606 twin pregnancies at the Johns Hopkins Hospital we<sup>4</sup> had a single case. Since approximately twenty-five per cent of twin pregnancies are monochorionic, the incidence from these two series is approximately once in 100 single chorion specimens."<sup>14</sup>

### Report of Case

The patient, a 35-year-old white para o-o-iv-o,\* was admitted to the hospital in early active labor one month prior to expected date of confinement. According to the menstrual history the expected date of confinement was March 9, 1942. Membranes had ruptured some thirteen hours previously. Significant only in the past history was the occurrence of the four early abortions about the sixth week of gestation from an unknown cause. The family history revealed no known multiple pregnancies on either side. The prenatal course was negative except for

\*First digit denotes the number of full-term pregnancies, the second the number of prematures, third the number of abortions, last figure the number of living children.



slight ankle edema in the afternoon in the last six weeks of the pregnancy. General physical examination was negative. The height of the fundus was 27 cm. and enlarged beyond the size expected for the duration of the pregnancy, apparently containing twins. Hydramnios was present. Only one fetal heart could be heard. The anteroposterior and lateral roentgen examination revealed a twin pregnancy with one fetus, in frank breech presentation, normal in appearance; the other was interpreted as an anencephalic.



Fig. 1.—Anterior view of acardius. The rent at about the lower third is an artefact, having been made during delivery, and allowing omentum and sections of intestine to show through.

After an uneventful first stage of labor of approximately twelve and three-quarter hours, the patient was delivered of a normal six-pound male child by breech extraction with forceps applied to the aftercoming head. Thirty minutes later the acardius was delivered, breech presenting. Some difficulty was experienced in the delivery of the monster because of the configuration of the caudal end. (Fig. 1). The third stage was uneventful. A single placenta was expressed by Credé's method, but was unfortunately discarded without examination.

*Autopsy Report.*—The specimen consists of a deformed fetal mass weighing 1,450 grams (3 pounds 3 ounces) and measuring 14 by 7 by 36 cm. The cephalic portion is globular in shape, somewhat flattened anteroposteriorly, and tapers into a fused, fin-like, lower extremity. Along the lateral borders of the cephalic portion are rudimentary upper

extremities containing bony and cartilaginous substance and covered with skin. These extend out from the body of the specimen 3 cm. They each end in a clubbed nodular fashion with two recognizable fingers. Most of the cephalic portion is covered with fine reddish hair. A dimpled, puckered area is present ventrally 4 cm. above the umbilical cord. There are no recognizable eyes, mouth or nose, in connection with this dimpled area. The dorsal portion of this mass has an imperforate anus at the junction between the bulbous cephalic portion and the pelvis. A short stubby spinal column can be palpated running from the pelvis up into the amorphous mass. The caudal extremity is fused and ends in a tapering fin with several recognizable toes. Internal examination reveals plates of bone and osteoid tissue housing liquefied cerebral substance. A fluctuating sac is present inside of these unfused



Fig. 2.—Anterior roentgenogram of acardius clearly showing bony abnormalities.

bones denoting an hydrocephalus. No visible recognizable heart or lungs are encountered. No thoracic cavity is demonstrable. The large body cavity contains small intestine and recognizable cecum and colon, but these end blindly in the peritoneum. A remnant of liver is present and recognizable spleen. Two undescended testicles are present in the retroperitoneum but no kidney tissue is seen. Although the wings of ileum can be recognized, there is no pelvic cavity. The spinal column is fused with the lower common extremity. (Fig. 2.)

### Comment

The case described conforms in a number of respects to the general trend of cases previously reported in the literature. The patient gave a history of four previous abortions but no former multiple pregnancies.

As is usual with monstrosities, hydramnios was present. The healthy twin was delivered first, as previously pointed out in twelve of fourteen cases,<sup>9, 10, 12, 19</sup> with the breech of the acardius presenting and delivery being effected thirty minutes later. Since the abnormality is described as one arising from uni-ovular and monochorionic twins, the case again conforms in that the healthy twin was a male child and undescended testicles were identified in the acardius.

The author wishes to acknowledge the permission of Dr. John G. Onnen to report this case and expresses appreciation to Dr. C. G. Warner of the department of pathology, University of Maryland, School of Medicine, and University Hospital for the pathologic study.

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3823 CALLAWAY AVENUE

## DIPHTHERIA OF THE UTERINE CERVIX\*

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IN 1932 Eigen<sup>1</sup> reviewed the literature of vaginal diphtheria and reported an additional case. His studies revealed a total of 115 cases, of which only 72 had been confirmed by bacteriologic investigation. The youngest in the series was 5 months of age, death being due to toxic myocarditis. The eldest was 55 years. This also was fatal.

Since then cases of diphtheritic vaginitis have been reported in English by Lee and Van Saun,<sup>2</sup> who mention six cases which were not included in Eigen's study, viz., Bisdorn's observations of three sisters (1927), Mason's case (1927), and the case of Vasile (1924); Wallfield and Litvak<sup>3</sup>; Cantrell<sup>4</sup>; Grant<sup>5-6</sup>; Stout<sup>7</sup>; and Parks.<sup>8</sup> The majority of the cases described were of the secondary rather than the primary type. Furthermore, our study of the literature has failed to reveal an instance in which the manifestations of the disease were confined to the cervix uteri. We are, therefore, presenting data regarding a case in which the clinical diagnosis was *diphtheria of the uterine cervix*.

### Case Report

Mrs. F. T. M. (T-42-39594), aged 23 years, resident of New Orleans, was admitted to the Charity Hospital April 23, 1942, presenting a chief complaint of "whitish vaginal discharge." Menstrual index was 15 by 28 by 6-7. She gave a history of having had two pregnancies. The first terminated spontaneously at approximately two months almost three years prior to the present admission. The second resulted in a normal delivery of a 7-pound 1-ounce living, well-formed male, eighteen months ago. Slight dysmenorrhea has been experienced for many years, manifesting itself as cramps and backache. Headaches and breast pain are also frequently associated with the onset of the menstrual flow, the amount and character of which have not changed recently. The vaginal discharge, of which the patient complained, was not sufficient to cause her to seek medical advice. As a matter of fact, the only reason that she came to the hospital was that a health examination was compulsory for continuation of her job as a waitress. The person referring her for admittance recorded a diagnosis of "tumor of the cervix."

Historical review by systems disclosed no positive facts of note. Thorough interrogation failed to elicit any evidence of luetic or Neisserian infections.

Past history included tonsillectomy and adenoidectomy in 1936 as the only surgical procedures. Measles and pertussis, uncomplicated occurred during childhood. There had been no serious illnesses or injuries.

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†Now on military leave of absence.

At 20 years she married for the first time. During this marriage the two gestations mentioned previously occurred. After a divorce, she married again on February 1, 1942.

Physical examination disclosed a well-developed and nourished ambulatory white female apparently not ill. Blood pressure, temperature, pulse, and respiratory rates were well within physiologic limits. The general physical examination was negative. Perineum was relaxed, but not lacerated. Skene's and Bartholin's glands showed no infection. The vaginal mucous membrane presented a healthy color. The non-irritating discharge was of a mucoid character. The cervix uteri exhibited an extensive frosty-white membrane which was firmly adherent to both anterior and posterior cervical lips. Attempts to remove portions of the membrane resulted in bleeding. The appearance was such as to cause the examiner to record the impression that it was diphtheritic in type. (At that time the patient was questioned fully regarding any treatments which might have been undergone during recent months to rule out the possibility of therapeutic traumatic cervicitis.) The very slightly enlarged uterus was in a state of third degree retroversion and beginning prolapse. It could be moved without difficulty and there were no abnormal adnexal masses. The rectal findings were irrelevant.



Fig. 1.—Frosty-white densely adherent membrane on anterior and posterior lips of cervix uteri, as seen at the time of admission to hospital.

Blood sedimentation rate proved to be 18 mm. in 3 hours, Linzenmeier method. Kline and Kolmer blood tests were negative. There was evidence of slight anemia, with a leucocyte count of 7,000, 84 per cent polymorphonuclear neutrophils. Urinary and hemochemical findings were within normal limits. Urethral, vaginal and cervical smears were negative for gonococci, trichomonads, and yeast.

Cultures of material from the cervix proved to be as follows: unsatisfactory, 4/30/42; positive for *Corynebacterium diphtheriae*, 5/5, 5/8, 5/11, 5/18, 5/26, and 5/28/42. On 6/1/42, they were negative and continued to be. Fig. 2 is a photomicrograph of culture from the cervix showing the typical palisade arrangement of *C. diphtheriae* with characteristic metachromatic granules, club-shaped forms, a few barred forms, and an occasional solid staining form. Subcutaneous virulence test employing pure culture of organisms obtained on 5/5/42 showed nontoxin producer. Intracutaneous virulence test employing pure culture of

organisms obtained 5/18/42, using a modification of the technique described by Fraser and Weld (1926) also demonstrated a nontoxin producer. Nose and throat cultures were negative for *C. diphtheriae* on 5/8/42, 5/11, and 5/13. Microscopic study of tissue obtained from the cervix on two occasions exhibited the picture of chronic cervicitis. Nose and throat cultures from the husband of the patient were positive for *C. diphtheriae* on 5/8/42, 5/11, and 5/18. Similar cultures from the little son were negative. Intracutaneous virulence test (Fraser-Weld modification) employing pure culture organisms obtained from nose and throat of patient's husband on 5/18 revealed a nontoxin producer.

On 5/10/42, after the patient had been proved not to be hypersensitive to diphtheria antitoxin, she was given 10,000 units intramuscularly. No local therapy was administered. A week later the membrane continued to grow, regenerating at the sites of removal; consequently, normal saline douches were given once daily. On 5/21/42, an additional 10,000 units of antitoxin were injected into the gluteal region, following desensitization procedure. Soon thereafter the membrane began to disappear, being completely gone four days later and leaving a cervix which presented erosions and eversion. Cultural studies proving to be negative, the patient was anesthetized with pentothal sodium and the areas of cervicitis destroyed by means of electrodesiccation. The patient was discharged from the hospital on the following day. Subsequent follow-up studies have revealed entirely satisfactory findings.



Fig. 2.—Photomicrograph of organisms cultured from the cervix, showing the typical palisade arrangement of *Corynebacterium diphtheriae* with characteristic metachromatic granules, club-shaped forms, a few barred forms and an occasional solid staining form.

Authors<sup>9-17</sup> of the current textbooks on pediatrics, obstetrics, and gynecology have little to say regarding diphtheria of the genital tract. They evidently concur in the belief that such infections are very rare. There are no data indicating that the infection can be transferred to the fetus in utero. And it should probably have no immunity; therefore, such an infant should be isolated and given the benefit of antitoxin. Negative Schick tests indicate that approximately 90 per cent of newborn babies have an immunity to the disease, but this protection is lost in most instances during the first year of life.

Before the introduction of aseptic methods in the practice of obstetrics, puerperal ulcers are said to have been very common. As a result of necrosis their appearance was such as to often cause them to be desig-

nated as "diphtheritic" although they had nothing else in common with diphtheria.

### Summary

The case of a 23-year-old white female who presented a frosty-white markedly adherent uterine cervical membrane is reported. The organisms cultured were morphologically *Corynebacterium diphtheriae*. Although virulence tests proved the organisms to be nontoxin producers, the administration of diphtheria antitoxin to the patient resulted in the disappearance of the cervical lesion.

Study of the literature confirms the opinion that female genital diphtheria is rare. Not a single case of diphtheria confined to the cervix uteri was found.

Every case of diphtheria should be given the benefit of careful study of the genitalia. Such studies in the past would have undoubtedly revealed some secondary infections which were overlooked.

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## STRUMA OVARIi

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**I**N GENERAL, 80 per cent of ovarian tumors are cystic and 20 per cent are solid. Dermoid cysts constitute about 10 per cent of the cystic tumors. The incidence of thyroid tissue found in dermoid cysts has been stated to vary from 1.5 per cent to 28.5 per cent.<sup>1</sup>

In 1928, Frankel and Lederer<sup>2</sup> gathered 50 cases of struma ovarii from the literature. In 11 of the 50 cases, thyroid tissue made up the whole tumor, but in only 2 cases was an associated goiter present.

The origin of mixed ovarian tumors affords a tempting field for speculation. At the present time the tendency is to refer to both cystic and solid ovarian tumors as teratomas, but to distinguish them on the basis of their physical characteristics. A cystic teratoma is defined as a tumor arising from all three fetal layers, in which the tissues are arranged in a more or less orderly fashion, and in which the structures arising from a single tissue type, the ectoderm, are usually predominant. A solid teratoma of the ovary is defined as a tumor which likewise arises from all three germinal layers, but in which the tissues are singled together indiscriminately and represent for the most part an embryonic development. Clinically, the chief point of interest is that, the dermoid tumor is benign, while the teratoma is malignant.<sup>3</sup> Piek<sup>4</sup> first advanced the theory, now generally accepted, that struma ovarii is a one-sided teratoma in which the thyroid had dominated or completely supplanted the elements of the other germ layers.

Because of its comparative rarity and interest, the following case is reported:

Hosp. No. 147758. J. S., aged 52. Admitted to the Bronx Hospital (service of Dr. Sidney Cohn) on July 12, 1943, because of rectal pressure, frequency of urination, associated with a sense of "fullness" in the perineum. Two weeks before she was examined an abdominal tumor was diagnosed. There were no other complaints.

Menstruation began at the age of 13 and had been regular about every thirty days. She had had her menopause about 2 years ago.

### *Physical Examination:*

She was a healthy looking adult woman. There was a harsh systolic murmur heard at the apex. Blood pressure was 130/85. There were no other abnormalities except a large insensitive cystic mass filling the left lower abdomen. Vaginal examination disclosed a small cervix and uterus with this large mass extending into the pelvis and displacing the left ovary. No enlargement of the thyroid was made out. There were no clinical signs of hyperthyroidism or hypothyroidism.

### *Preoperative Diagnosis:*

Ovarian cyst, left.

### *Operation:*

Performed on July 13, 1943, under spinal anesthesia. The left ovary was found to be replaced by a multilocular cyst, some of which was solid. A left salpingo-oophorectomy was performed.



*Pathology:*

No. 25269. Specimen received consisted of a tube with its attached ovary. The tube measured 12 cm. in length and showed no gross pathology. The ovary measures 17 by 12 cm. in size. The external surface was smooth and yellowish-white in color. On section it was multilocular and the loculi for the most part contained serous material. Some, however, contained sebaceous material. Areas of fleshy soft brownish homogeneous tissue, resembling thyroid tissue, were also visible.

Microscopic examination showed a portion of ovarian tissue intimately related to a mass of well-defined thyroid tissue in which the acini varied in size and contained colloid in profuse amounts (Fig. 1).



Fig. 1.—Path. No. 25269. Section through ovarian cyst wall, showing thyroid tissue.  
X300.

*Diagnosis:*

Struma ovarii in a dermoid cystoma.

Patient had an uneventful hospital stay and was discharged on the twelfth postoperative day. Examination at the end of 4 weeks showed no abnormal findings. Basal metabolic rate was plus 5.

We wish to express our appreciation to Dr. Joseph Felsen, Director of Laboratories, the Bronx Hospital, for his aid in the preparation of this report and for the photomicrographs.

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## UNILATERAL TWIN ECTOPIC PREGNANCY

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PREVIOUS reports have established the validity of 72 cases of unilateral twin tubal pregnancy.<sup>1-5</sup> The last reported was that of Lash and Kaufman in 1942.<sup>6</sup> We wish to add another to this group.

The patient, a 33-year-old married, colored female was admitted to the Hospital of the University of Pennsylvania on April 27, 1943. She had had five normal full-term uncomplicated pregnancies between 1927 and 1937, followed by two spontaneous abortions in 1937 and December, 1942. Her menses had always been regular with a moderate amount of flow. Dysmenorrhea had always been mild at the onset of her periods. Past history was negative.

The patient's last normal menstrual period was on February 10, 1943. On March 15, 1943, she noted the usual amount of bleeding for a normal period except that it was five days late and that it lasted two weeks. During this time she had indefinite, diffuse, lower abdominal cramp-like pains. Following this she felt well until April 1, when the cramps returned to be associated with vomiting which continued up to the time of admission to the hospital. On April 23, she had a small amount of vaginal spotting for only one day. After March 15, bleeding episode, she had had a moderate amount of a persistent, non-odorous white vaginal discharge. There had been no shoulder or chest pain, fever or chills, fullness of the breasts, urinary frequency or fainting attacks.

When admitted to the hospital, the patient appeared rather weak and seemed to be suffering from a moderate amount of lower abdominal pain. Colostrum was present in the left breast. Temperature was 99.5° F., blood pressure 124/80, pulse 68, and respirations 17. There was a mild, soft abdominal distention. On pelvic examination, the cervix was found softened, appeared normal in color and clean. The uterine fundus was anterior, slightly softened and very slightly enlarged. The right adnexal area was negative to palpation. There was a doughy, tender, partially movable mass high in the left adnexal region approximately 6 centimeters in diameter. The hemoglobin was 68 per cent, white blood count 6,800, catheterized urine specimen showed only an occasional red blood cell. Kolmer and Kline tests were negative.

A diagnosis of left tubal pregnancy with tubal abortion was made and laparotomy advised. At operation the uterus was found to be softened and enlarged to the size of a six weeks' gestation. The left tube and ovary were surrounded by a few fine and dense adhesions. The left tube appeared normal. The left ovary was approximately 5 centimeters in diameter and contained a retention cyst. The right tube was moderately thickened and closed at its fimbriated end. In the middle third, it was enlarged and adherent to that portion of the ovary which lay below the tube. Both were plastered against the posterior leaf of the broad ligament. Contained within this portion of the

tube and the wall thereof, and the upper pole of the ovary was a mass of tissue containing two small fetuses. There was a small area of rupture on the right lateral side of the mass from which blood apparently had been leaking to partly fill the cul-de-sac of Douglas. About 200 c.c. of dark blood was present. There was a dull blue discoloration of the omentum and intestines in this area. The mass was surrounded by a large number of fine and dense adhesions. The operation was completed by freeing the adhesions and performing a routine right salpingo-oophorectomy. The abdomen was closed without drainage.

The gross pathologic description: "The specimen consists of the right tube and right ovary and two fetuses. The right tube and ovary form a mass measuring 8.5 by 7 by 2.5 cm. in diameter. The right tube is approximately 13 cm. in length. The outer two-thirds is dilated to a diameter of 5 cm., is hemorrhagic and shows a perforation on the posterior wall. Protruding from this perforation is an old blood clot. In this area the tube wall is markedly thin, giving the typical appearance of a ruptured tubal pregnancy. The right ovary lies in the concavity of the tube and measures 4 by 3.5 by 1.5 cm. in diameter. The superior portion of the ovary is adherent to the tube at the site of the perforation. The ovary shows perioophoritis, otherwise is normal. The fetuses which were removed from the right tube at operation measure 6.25 and 6.5 cm. in length respectively. Grossly these show no abnormalities."

The microscopic diagnosis was right tubal pregnancy; right perioophoritis. "Sections from the right tube show the wall to be markedly thin. There is typical placental tissue noted invading the wall of the tube. Sections from the ovary show perioophoritis."

Her postoperative course was uneventful except for a moderate increase in postoperative reaction with vomiting and distention for the first three days. The wound healed by primary union. She was discharged on her thirteenth postoperative day in good condition.

### Comment

The mass that was palpated in the left adnexal region was not that of the ectopic gestation but a retention cyst, while the right side containing the real pathology was negative to bimanual palpation. These findings were confirmed also by three other examiners.

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## PELVIC ABSCESS FOLLOWING ARTIFICIAL INSEMINATION

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THE treatment of relative infertility has taken on new interest in recent years as a result of certain fundamental contributions to our knowledge on the subject. The insufflation of the tubes as described by Rubin for the determination of tubal patency, the study of the endometrial biopsy for the determination of ovulation, and careful study of the seminal fluid are but a few of the more recent diagnostic aids that have been introduced for the management of the sterile couple. The latter of these has instituted a wave of enthusiasm for artificial insemination of the alleged defective seminal fluid into the cervix and often into the uterine cavity to overcome sterility which is thought to be due to failure of the sperm to migrate into the uterus under their own power. The fact that a defective seminal fluid is most probably not capable of fertilizing the ovum even if it were deposited directly upon it is a factor often forgotten. Indeed the indiscriminate use of the husband's seminal fluid for injection into the uterus is most vehemently to be condemned. Indications for artificial insemination have been laid down by Guttmacher and in substance they are: anomalies of the male genitalia which make it impossible to deposit the seminal fluid near the cervical os at coitus; anomalies or atresia of the vagina which makes coitus impossible and therefore the seminal fluid cannot be deposited near the cervical os. In the case to be reported the husband had a normal seminal fluid, both in amount and morphology but had never been able to have an erection of the penis. The seminal fluid was readily obtained by the patient in a manner which he did not divulge but his wife insisted that introduction of the penis into the vagina had never occurred during their seven years of marriage.

Mrs. M. C., aged 29, gave a history of good health throughout her life. The menarche occurred at 14, and after a few months of irregularity a regular cycle was established. She was married for six years at the time of the first examination and her only complaint was sterility. The marital relation had never been satisfactory because of the failure of her husband to maintain an erection sufficiently long to introduce the penis into the vagina. She stated that coitus had never been accomplished. A complete sterility study revealed a normal secretory endometrium at the onset of 3 consecutive menses, the vaginal pH was 4.8, the basal metabolic rate was  $-8$ , the tubes were patent but at a relatively high pressure on the first examination. Subsequent tests showed the tubes patent at 125 mm. of mercury. The pelvic organs were normal in size, position and contour. The seminal fluid was examined from a sterile bottle into which the patient's husband had ejaculated. The quantity was 4.1 c.c., the motility was normal (85 per cent motile forms), and the morphology was normal (12 per cent abnormal forms). Since the failure to deposit the seminal fluid into the region of the cervical os was apparently the only sterility factor, the patient was advised to come to the office for artificial insemination. Study of the endometrial biopsy suggested that ovulation apparently occurred about

the eighteenth day of her cycle and this coincided with the patient's history which was fairly good for the "*mittelschmerz*." She was inseminated for 3 successive months and pregnancy did not occur. At this time the patient disappeared only to return about 6 months later requesting further insemination. On October 2, 1943, the patient was inseminated by the author. At the time she complained of some cramping and I knew that some of the fluid had entered the uterine cavity. The canula was withdrawn and the rest of the fluid deposited in the cervical canal. She called that evening complaining of low back pain. Two days later the temperature went to 100° F., and on the sixth day after insemination the temperature went to 100.8° F. Pelvic examination revealed a generalized induration and tenderness radiating out into the pelvis from the cul-de-sac. The patient was treated for 12 days with maximum doses of sulfadiazine with no apparent effect. At this time she was admitted to the hospital where after 7 days of bed rest the abscess localized and a fluctuant mass could be palpated in the posterior vagina. This was incised and drained and with finger dissection a large volume of pus evacuated from the cul-de-sac and a "T" tube placed in the region of the broad ligaments. At this time the abscess could be palpated 5 cm. above the symphysis. Six days later the patient ran a normal temperature, the abscess cavity rapidly became reduced in size and on the eighteenth day after operation the "T" was expelled from the vagina. On discharge from the hospital the pelvis was full of adhesions but the tenderness and mass had disappeared.

The future of this patient so far as fertility is concerned is not very bright. Thus there is illustrated again the favorite aphorism of Dr. DeLee "*prima nix nocere*" illustrated in a paradoxical sort of way. It is to be re-emphasized that a sterile seminal specimen is most difficult to obtain and even when the most scrupulous care is used to inseminate it with aseptic technique, the tragedy above described may be re-enacted.

MEDICAL ARTS BUILDING

## NAEGELE PELVIS ASSOCIATED WITH RUDIMENTARY FEMUR\*

PHILIP B. WAHRSINGER, M.D., NEW YORK, N. Y.

(From the Obstetric Service of the Bronx Hospital)

THE most common cause of the Naegele pelvis, according to DeLee, is disease of the sacroiliac joint and the neighboring portions of the ilium and the sacrum. Other authors give diseases of the hip joint, arthritis, caries, or trauma of the sacroiliac synchondrosis as causes of this type of pelvis. Congenital anomalies may also be the cause of this pelvic deformity. It is because of the rarity of the anomaly of rudimentary femur as a cause of Naegele pelvis that the following case is report.

E. S. (Hospital No. 145,765), a 21-year-old primigravida was admitted to the prenatal clinic of the Bronx Hospital with a history of having had her last menstrual period on August 25, 1942. Her expected date of confinement was calculated as June 1, 1943. The height of the fundus was commensurate with the date of the last period. It was noted that the patient had a congenital abnormality of the right lower extremity and hip. The right foot was at the level of the left knee. Measurement of the pelvis showed the following. Interspinous 24 cm., left oblique 16 cm., right oblique 23 cm., external conjugate 20 cm., transverse of the outlet 11 cm., depth of the symphysis 4 cm., diagonal conjugate 12½ cm. The pubic arch was obtuse.

Upon questioning, the patient gave a history of some orthopedic operation in early childhood. The following information was obtained from the surgeon, Dr. J. B. L'Episcopo, who had performed the operation in November, 1927.

"The patient had a congenital absence of the upper part of the right femur. A knee joint was present but there was a very rudimentary lower part of the femur. An operation was performed in which the side of the ilium was turned down and the rudimentary femur was brought up against it in order to permit weight-bearing of the femur against the side of the ileum."

Following an uneventful prenatal period the patient was admitted to the hospital in active labor at term. Examination at this time showed the vertex presenting but unengaged. The membranes were intact. In view of the above mentioned abnormality an orthopedic consultation was requested. This report by Dr. S. W. Boorstein was as follows:

"The right lower extremity shows no motion at the hip. Motion is present at about one to one and a half inches below the hip where there is a rudimentary knee joint. The right lower extremity is fifteen inches shorter than the left and the right foot is at the level of the left knee. The patient gets about with an artificial limb."

\*Presented at a meeting of the Section on Obstetrics and Gynecology of the New York Academy of Medicine, December 28, 1943.

Because of the pelvic deformity in the presence of active labor with the head unengaged x-ray pelvimetry was ordered. The report by Dr. William Snow was:

"Radiographic examination of the abdomen shows pregnancy in vertex presentation. The head is in the left occiput transverse position dipping at the inlet. The fetus appears to be rather large. The placenta is located anteriorly. The pelvis is platypelloid. In addition there is asymmetry. The right forepelvis is shallow. The latter condition is due to the fact that a congenital malformation was present in the right lower extremity. The right femur is rudimentary. On the film it measures approximately eight centimeters in length. The false acetabulum is present just above the usual level. The tibia and fibula are of fairly normal appearance. The foot reaches to the level of the knee on the other side."



Fig. 1.—X-ray showing rudimentary femur, also tibia and fibula on right side.

#### Pelvimetry:

Pelvic Inlet	True conjugate	9.7 cm.
	Transverse	14.0 cm.
Midpelvis	Anteroposterior	10.1 cm.
	Interspinous	11.5 cm.
Outlet	Posterior sagittal	9.4 cm.
	Intertuberosity	10.8 cm.

Notwithstanding the x-ray findings, it was felt that this patient would be able to give birth by the vaginal route. Following a total labor of twenty-three hours, the patient was delivered spontaneously of a living six-pound fourteen-ounces female child. The baby was normal in all respects. The patient was discharged on the ninth post-partum day following an uneventful puerperium.

This case has been presented as a case of obliquely contracted or Naegele pelvis as a complication of the rare congenital anomaly of rudimentary femur.

1229 CLAY AVENUE

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Beruti, Josue A.: The Problem of Natal Mortality, Arch. Clin. obst. y ginec. "Eliseo Canton" 1: 29, 1942.

Josue A. Beruti (Buenos Aires) in an introduction to a subsequent statistical study, discusses natal and neonatal mortality as factors involved in the declining birth rate in Argentina. Although infant mortality in general has decreased markedly, there has been an alarming increase in neonatal mortality. Twenty-five per cent of all infant deaths occur during the first three days of life. The author considers that stillbirths should also be included in a study of infant mortality and that gynecologists and obstetricians should be concerned with the possibility of reducing their incidence by more intensive application of the principles of hygiene, preventive medicine, obstetrics and pediatrics. Because of varying definitions of natal mortality, official statistics on the subject are hopelessly confused. In Buenos Aires a lapse of three days is allowed between birth and registration, thus death of a child within this time is recorded as a stillbirth. The author defines the categories which he uses in his statistical study. A viable child born without heartbeats is considered a stillbirth; a child of less than 2,500 Gm. is called premature; "newborn" includes birth to one month.

According to statistics published in the bulletin of the Panamerican Health Office, Feb. 1, 1940, there are few American (N. and S.) countries and cities which have shown a regular and continued decrease in natal mortality, many of which have shown an increase and most showing no definite increase or decrease. Statistics for Buenos Aires (Municipal Statistical Review) during the period 1914 to 1939 show in general a descending tendency (maximum 1923, 5.3 per cent, and minimum 1939, 2.6 per cent). The decrease is almost constant since 1927 and absolutely constant since 1934. According to De Rudder, the neonatal mortality of the world has increased slightly.

Different laws and customs governing registration of births, differing criteria for determining stillbirths and laxity in reporting births contribute to inaccuracy even in official statistics. In hospitals, especially children's hospitals and maternity centers, the more careful records and better discrimination as to the causes of fetal or infantile deaths make statistics from such sources more valuable, but with its accumulation of complicated cases a hospital does not adequately represent a province or locality. For this reason the statistics which the author is to present, although based on a great number of cases, represent a particular situation. A more complete picture could be obtained only by combining statistics from all maternity centers of all cities and towns in the Republic. Since this is at present Utopian, he confines himself to an investigation of the clinical material from one maternity center in Buenos Aires, hoping that this combined with material from other institutions may yield some instructive facts. The author warns that the statistics are not absolutely perfect since the clinical records, especially in early years, are not all satisfactory and since diagnostic, prophylactic and therapeutic criteria have not remained constant through the years.

J. P. GREENHILL.



## SPECIAL RUBBER GLOVE WITH SCALE FOR MEASURING THE TRUE CONJUGATE DIAMETER

H. B. BISCOW, M.D., NEW YORK, N. Y.

THE present accepted method of measuring the true conjugate is for the physician to introduce his middle and index finger into the vagina, place the tip of the middle finger on the promontory of the sacrum, and with the finger of the other hand, close to, or a little under the symphysis pubis, mark off the space, withdraw his hand, and have an assistant place the two points of the metal pelvimeter on the two ends of the marked off space. From this marked off space, must be subtracted  $1\frac{1}{2}$  to 2 centimeters to allow for the thickness of the symphysis pubis. After the subtraction is made, he obtains the length of the true conjugate.

To simplify this procedure, the rubber measuring glove is offered.

This is an ordinary rubber glove which has a measure printed on the side of the index finger, in centimeters, inches, or both. The measurement is taken in the usual way.

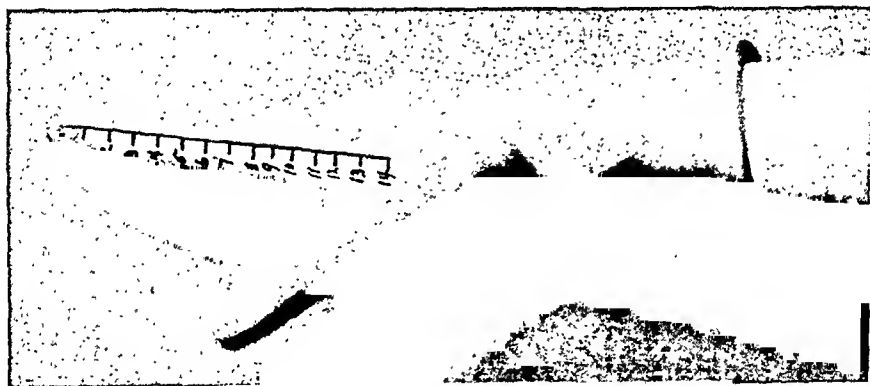


Fig. 1.

1. Measure the diagonal conjugate. Place the tip of the middle finger on the promontory of the sacrum. Mark off the under border of symphysis pubis by finger of the other hand.

2. Read measurement on the centimeter scale on index finger of the examining hand which will give the length of the *true conjugate* and not the diagonal.

3. This is so because the difference of the length between the tip of the middle finger and the tip of the index finger is approximately the thickness of the symphysis pubis.

The advantages of this measuring glove are: 1. Simple, 2. Direct, 3. No need of an assistant, and 4. Always at hand.

## Editorial Comment

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### NONBIOLOGICAL FACTORS AFFECTING SUCCESSFUL HUMAN CONCEPTION

**I**T MAY be claimed, perhaps, that the days of the obstetrician, confining his work solely to the mechanics of obstetric care, are numbered. At least manifold compilations of figures and facts appertaining to maternal and infant mortality have brought about a reduction in the number of radical midwifery maneuvers. Cumulative statistical evidence placed in the hands of maternal and child health agencies and our specialty has compelled sound revision in obstetric method, technique, and judgment.

Within the recent two decades numerical realities, concerning maternal and infant morbidity and mortality, have dictated new codes of ethics in maternity hospitals. Laws concerned with the safety of mothers and the newborn were placed upon the statutes of many states. Large cities have decreed health ordinances persuading the attention of less careful physicians to the problem of prematurity.

Obstetricians, as a class of sincere specialists, heeded these warnings of the biometric analysts. Obstetrical care in the ante-partum, intra-partum and post-partum periods was tremendously improved from this statistical impetus. We must admit, however, as do some of our leaders with becoming distaste, the ultimate solution will be found only in educational programs for the new generations of physicians *and the populace*.

As clinical specialists we must further confess that the statisticians are far ahead of the teaching obstetricians in their constant search for significant biometrical correlations. How many of our obstetric divisions, within university centers, have recognized the inclusion of premarital advice, psychosexual problems of pregnancy or the socioeconomic significance of abortion in their curricula? It remained for the sciences of humanity to acknowledge the contributions of the biometric analysts. Sociologists are teaching premarital advice. Sex education is being stressed by the psychologists and authorities dealing with delinquency problems. The psychosomatic problems in pregnancy (illegitimacy, postabortal sequelae, conversion neuroses and others) are being unravelled by the social workers, the welfare bureaus and judicial agencies.

Since the onset of World War II, there is an increasing amount of still more overwhelming statistical evidence to warn the physician that his services, as an obstetrician, must be increased. Facts, figures and graphic demonstrations concerning policies of population, differentials in human fertility, social and psychologic factors affecting human fertility are being collected, collated and published. The obstetrician of tomorrow must learn the newer biometric jargon. He must intelligently understand, evaluate and apply these truths to his practice.

The Milbank Memorial Fund and the Carnegie Corporation of New York City financed recently, at considerable expense, an extensive survey of the social and psychologic factors affecting fertility. A specially selected research group, without, however, representation of the obstetric group, was formed to study these problems. This new group is banded under the lengthy title of a *Committee on Social and Psychological Factors Affecting Fertility*. As obstetricians and gynecologists it is well worth our time to consider their early reports.

One of the first reports\* emanating from this Committee concerns itself with the differential fertility among 41,498 native white couples in Indianapolis. Nine pages of this fifty-eight-page report are devoted to statistical evidence listed as proof of the report's demographic and biometric accuracy. The summary is given two and one-half pages. These workers made certain interesting observations. They report: among other things that "Catholic couples are 18 per cent more fertile on the average than Protestant unions—" while "mixed Protestant-Catholic marriages on the other hand are 10 per cent less fertile than Protestant unions." The Jewish couples, 419 or 1.0 per cent, constituted "but a small sample." The conclusion drawn however states that "they are 25 per cent less fertile on the average than the Protestant couples."

The most sweeping conclusion of the Whelpton-Kiser report states, "In general, the traditional inverse relation of fertility to socio-economic status is found for both Protestant and Catholic marriages. This is true in the analysis of fertility by rental value of the dwelling unit, rent paid by the couple, and educational attainment of the husband and wife." The investigators report one exception to this conclusion. "In the rental group above the \$50-\$59 level the fertility rates increase with rising rental level."

Education as a "factor affecting fertility" disclosed "on the basis of the wife's education that the fertility rate for Catholic couples exceeds that for Protestant couples by 40 per cent at the college level, but by only 3 per cent at the grammar school level." When the husband's education is considered "the comparable figures are 39 per cent and 7 per cent."

The region of the couples' birth seems to "affect fertility" for among the "Protestant unions by birth region of the husband and wife yield the lowest fertility rates for the northern born couples and highest rates for the southern born." The statisticians have performed a superb job of collating objective statistical evidence for one city. These findings, for the most part, could have been predicted by any experienced obstetrician in Indianapolis. Little new information is added. Old generalizations were simply categorized and pigeon-holed in their proper percentage parcels.

The study on "social and psychological factors affecting fertility" illustrates several fallacies of the sociologic statistician. For the most part these investigators attempt objective analyses of medical problems with but little knowledge of medicine or medical nomenclature. In their earnest efforts to explain the correlations new definitions are developed. We witness terms such as "differential fertility," "fertility rates," "children per 100 wives," "age specific fertility rates" being added to our nomenclature. Their preciseness and impecceability,

\*Whelpton, P. K., and Kiser, C. V.: *Milbank Memorial Fund Quarterly* 21: 221-280, 1943.

characterized in the graphs and statistical tables, loses its effectiveness with loose and faulty choice of medical terminology.

In the title of their report, namely, *Social and Psychological Factors Affecting Fertility*, the statisticians give a totally different meaning to the word fertility than would be ascribed to that connotation by obstetricians. The statisticians say they measured "factors affecting fertility." They actually measured successful conceptions and some factors which were directly or indirectly proportional to accomplished fertilization and successfully terminated pregnancies. While social and psychologic factors may reasonably be expected to affect the reproductive histories of couples, it is difficult to see in what possible manner being poor, northern-born, or Catholic could influence the motility of spermatozoa or the incidence of cyclic ovulation. Fertility, to the medical world, connotes the potential or real ability of an individual who possesses the biologic capability of contributing 50 per cent of fertilizable germ cell plasma essential to effect a fertilized ovum. Obviously education, religion, the socio-economic status, and our moral training contribute to our volition in determining whether or not the implantation of fertilizable spermatozoa occurs during the ovulatory period in a specific coition. But obstetricians will disagree that intrinsic biologic fertility can be changed by such extrinsic forces. A normal woman's ovaries contain eggs and a normal man's testicles develop sperm, be she or he poor or rich, agnostic or believer, brilliant or dull, or an urban or rural resident. As scientific men we must protest the misuse of the connotation fertility as used by statisticians.

As obstetricians we generally concede that approximately 70 per cent of pregnancies occur in the third decade of life, ages 20 to 29 years. This age group in the Whelpton-Kiser report constitutes 40 per cent of their entire series of 41,498 wives. It is difficult therefore to agree upon the general conclusions regarding "factors affecting fertility" among these women who have not yet completed their reproductive lives. In all figures developed, it is plain that percentages and conclusions obtained by using the common divisor 41,498 cannot hope to be statistically sound. In all fairness to these excellent reporters, they have broken the age group down into multiple smaller collated analyses, although the significance of these secondary conclusions becomes weaker by virtue of the small numbers.

Whelpton and Kiser performed a splendid work in their painstaking analysis. They have pioneered a pattern for statistical evaluation of realized human conceptions. They presented the first complete statistical picture of realized term pregnancy in a large city during a specific period of time. Undoubtedly other reports emanating from this same survey will consider abortion, illegitimacy, divorce, separation and other concrete factors affecting human reproduction within a specific region. It is to be hoped they will seriously consider the addition of experienced obstetricians to their advisory staff before they publish more data upon the subject of human reproduction.

The specialty of obstetrics and its leaders will profit when more attention is paid to the social and psychologic factors which may leave the individual obstetrical episode a moment of either happiness or tragedy to the family unit. The psychosomatic aspects of pregnancy must be considered if we are to lessen maternal and infant morbidity and mortality. Our obstetric savants must heed the voices of the biometric analysts who labor so diligently that our population may reach biologic sound qualitative and quantitative levels. Physicians can

assist in reaching an ideally balanced population attainable with the least human misery and compatible with the most decent living standards.

In reiteration we must conclude that the days of the obstetrician, confining his work solely to the mechanics of obstetrical care, are numbered. The modern obstetrician is expected to be familiar not only with the physiology, biochemistry, histology, pathology, and metabolism of pregnancy, but also with the social, psychiatric, economic, and psychologic factors affecting reproduction. The evaluation of these latter factors can be reached only through a considered inventory of them. The obstetrician owes much to the statistician. They should know one another.

CLAIR E. FOLSOME, M.D.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Puerperium Labor, Complications

Valhor, B.: Rupture of the Aorta in the Puerperium, *Acta. obst. et gynec. Scandinav.* 21: 417-426, 1942.

Rupture of the aorta during pregnancy, labor or the puerperium is a rare condition. There are only fourteen cases reported in the literature. Most of these were spontaneous. The author reports a case which occurred in Stockholm on the fifteenth day of the puerperium. Death occurred seven days later.

J. P. GREENHILL.

Cairns, D. R., and Melton G.: Primary Thrombosis of Cerebral Veins in the Puerperium, *Brit. M. J.* 1: 439, 1942.

A case of possible thrombosis of cerebral veins is reported to have occurred in a 29-year-old, white secundipara. She was admitted late in the puerperium of her second pregnancy because of severe anemia following post-partum hemorrhage at the time of her delivery. She was transfused without incident. On the seventeenth post-partum day she had three convulsions, followed by one more on the next day. There was no aura, nor was there any elevation of blood pressure. The convulsions were followed by nausea, vomiting and headache. The spinal fluid contained blood and the pressure was elevated. There were localizing signs in the left hand. Recovery was gradual but complete. While such a syndrome may exist, it is the opinion of the abstractor that it is not proved in this instance.

F. M. HELLMAN.

### Puerperium

Gunther, Mavis M. B.: Lactation in Women, *Canad. M. A. J.* 47: 424, 1942.

In this paper an attempt is made to correlate clinical experience in interpreting the problems of nursing with the physiologic background of lactation. The author supports the view that the response of the mammary gland to pregnancy is due largely to the action of estrogens. Progesterone also plays a part in the breast development, for it can be demonstrated experimentally that it has a synergistic action with estrogens. The secretion of the anterior lobe of the pituitary is recognized as necessary at least for the maintenance of lactation. The exact mechanism of initiation of lactation is not clearly recognized. The secretion of milk consists of two processes, a continuous one by the alveolar cells into the lumen of the alveoli and the ducts, and an intermittent one of removal from the gland. The author points out that regardless of the mechanism which limits secretion when the breasts are full, a period of not emptying reduces secretion very rapidly and when once reduced, the rate depends upon the demands made on the breast and its response to these demands.

The author recommends:

1. Putting the infant at breast within twelve hours of the delivery, and every eight hours during the next two days.
2. Limiting the nursing period to 1 to 2 minutes until adequate secretion is available.

3. Nursing at both breasts every four hours.

4. The omission of artificial feeding until after lactation has been well established.

CARL P. HUBER.

Boigen, A.: *Puerperium in Women Having or Having Been Operated Upon for Ovarian Cyst*, An. del Inst. de Mat. y Asis. Social 3: 1941.

The rare association of ovarian cyst and pregnancy is partly explained by the author by the fact that cystic ovarian tumors are an important fact in the etiology of sterility. The cyst may cause interruption of pregnancy, and per contra, the pregnancy may aid torsion of the pedicle of the cyst. In the first-half of pregnancy, ovariectomy is indicated; in the last half expectant observation with the possibility of intervention at the first sign of complications. Dystocia and uterine rupture may be caused by the presence of the cyst during labor. In a study of fifty-two cases in which the cystic ovary had been removed during pregnancy, no puerperal morbidity attributable to the operation was observed.

ROBERT J. WEISSMAN.

Schmidt, Harry J.: *The Use of Progesterone in the Treatment of Post-Partum Psychosis*, J. A. M. A. 121: 190, 1943.

The author reports a case of recurring post-partum psychosis coming on ten days after a normal delivery. The periods were definitely associated with her menstrual periods. An attempt was made to explain this on the sudden withdrawal of progesterone by the removal of the placenta, which would leave an excess of estrogenic hormone in the circulation. Therefore, physiologically, progesterone would be indicated for treatment, and it is felt that the early use of this hormone may be valuable in the prevention of post-partum psychosis.

WILLIAM BERMAN.

McIntyre, W. Keverall: *Further Notes on the Control of Post-Partum Hemorrhage by Injection of the Umbilical Vein*, Australia M. J. 2: 517, 1942.

The author reports his results in fifty-one cases in which he uses the cord injection method of treating cases with retained placenta. The author uses warm saline (115° to 120° F., when it reaches the uterus). A temperature drop of 10° F. is allowed for every 12 to 15 inches of cord. The uterus responds to saline at higher temperature than at room temperature. The solution is injected as rapidly as possible with a syringe. The average amount injected into the umbilical vein varied from 568 c.c. to 1,136 c.c.

In forty-three of these fifty-one cases, there was no morbidity during the puerperium. Eight patients had a mild temperature rise up to 100° F., which lasted a few days.

The author advises that the usual expectant treatment in the third stage should always be employed; but in certain cases the procedure should be used in anticipation of trouble, as in threatened uterine atony, or after intrauterine manipulations in the second stage. The author also advises its use in cases of steady hemorrhage from an atonic uterus.

WILLIAM BERMAN.

## Abortion

Javert, C. T., and Stander, H. J.: *Plasma Vitamin C and Prothrombin Concentration in Pregnancy and in Threatened, Spontaneous, and Habitual Abortion*, Surg. Gynec. & Obst. 76: 115, 1943.

Of 24,289 pregnant women admitted to the Woman's Clinic of the New York Hospital, 9.0 per cent had vaginal bleeding, and of this group 1 in 15 suffered complete or incomplete abortion.

In seventy-nine patients vitamin C levels were studied at the time of threatened, spontaneous or habitual abortion. The values formed in these patients were slightly below the normal control group. In the same cases the maternal plasma prothrombin concentration was measured. In this instance, it was significantly lower than that formed in the normal controls.

The authors, in treating spontaneous, threatened and habitual abortion, not only used diet regulation and vitamins C and K, but also hormones and minerals. Thus, the results are only suggestive that these two vitamins might help in prevention of abortion.

L. M. HELLMAN, LT. MC., USNR.

Leon, Juan: Therapeutic Abortion and Simultaneous Sterilization. Actual Value of Surgical Methods by the Vaginal Route, Arch. Clin. obst. y ginec. "Eliseo Cantón" 1: 113, 1942.

Juan Leon states that the opportunity to use surgical methods is found principally in the third month of pregnancy because evacuation of the uterus with the usual obstetric means at this time is difficult and dangerous, owing to the size of the ovum. An imperative condition for the success of the operation is that there is no contraindication to opening the peritoneal cavity through the vagina. Four techniques for vaginal cesarean section are available: vagino-cervico-isthmic, vagino-isthmic with longitudinal incision, vagino-isthmic with transverse or arcuate incision, and vagino-corporal. The last three, which do not involve the cervix, are preferable. If conditions allow it, they may be complemented by some method of permanent or temporary tubal sterilization. If the patient's general condition is bad, especially if pregnancy is somewhat advanced, it is better to defer sterilization. If the cervix is infected, opening the peritoneal cavity to perform sterilization may seriously endanger the life of the patient. Under the circumstances, the vaginoisthmic method is indicated, leaving sterilization for later, or the small abdominal cesarean section with simultaneous sterilization may be used.

J. P. GREENHILL.

Neuweiler, W.: The Frequency of Full-Term Pregnancy After Threatened Abortion, Schweiz. med. Wchnschr. 71: 1303, 1941.

Neuweiler followed up a series of eighty cases of threatened abortion. Only fifty of the women (62.5 per cent) went to term. This is a high incidence of success as compared with reports in the literature. It was interesting to note that 78 per cent of the women from farms went to term, whereas only 41 per cent of the urban women carried their babies to term. Strangely enough, most of the unmarried women (two-thirds) went to term, whereas among the married women the reverse took place, namely only one-fourth of the women went to term. The author emphasizes, therefore, that the outcome of abortions depends upon such factors as place of abode, civil and other conditions.

J. P. GREENHILL.

Schumacher, W.: The Indications for Intrauterine Manipulation, Schweiz. Med. Wchnschr. 72: 353, 1942.

The author treats patients who have febrile abortions conservatively for at least 24 to 48 hours. After the temperature drops, the uterus is emptied by curettage. In cases where there is suspicion of criminal abortion, nothing is done for at least five to eight days except to prescribe medication.



In a series of 408 cases, only twenty had complications. Two women died. Eleven of the twenty women had complications when they were admitted to the hospital, and only ten of the patients treated conservatively developed complications. In six cases, the trouble was extragenital. In the author's clinic all febrile abortion cases are given sulfanilamide.

J. P. GREENHILL.

Falls, Frederick H., Rezek, George H., and Benensohn, S. J.: *Clinical and Experimental Observations on the Use of Corpus Luteum Extracts in Obstetrics*, Surg. Gynec. & Obst. 75: 289, 1942.

The authors report the use of intramuscular and intravenous water extracts of corpus luteum for various obstetric conditions. In 452 cases of threatened abortion, they claim 83.5 per cent to 86.5 per cent success in contrast to 88 control cases treated palliatively with only 39 per cent salvage. Out of one hundred sixty cases of habitual abortion, there were seventeen failures. While the authors define "habitual abortion" as in a patient having two or more abortions, the tables seem to include many cases with only one previous abortion. The use of corpus luteum extract in forty-six cases of partial premature separation, eighteen cases of placenta previa, and eight cases of premature rupture of the membranes, with 91 per cent, 94.5 per cent, and 87 per cent terminating successfully, is also reported. Also the successful use of corpus luteum extract following laparotomy on pregnant women is described.

L. M. HELLMAN.

## Menstruation

Russell, P. M. G., and Dean, E. M.: *Influence of Thyrotoxicosis on Menstruation*, Lancet 2: 66, 1942.

Thyrotoxicosis, even when severe, may have no effect on menstruation. When it does affect menstruation, it tends to produce first scanty periods, and then amenorrhea, which was present in over half of the twenty-nine severe cases in a series of one hundred thirty-nine. Where the periods had become scanty, or absent, they returned to normal in about half of the cases operated on. Menorrhagia is uncommon in thyrotoxicosis, and is probably transient when it does appear.

CARL P. HUBER.

## Anesthesia and Analgesia

Adams, R. Charles, Lundy, John S., and Seldon, Thomas H.: *Continuous Caudal Anesthesia or Analgesia*, J. A. M. A. 122: 152, 1943.

The authors report their use of the modified Hingson-Edwards technique of continuous caudal anesthesia. They use a No. 5 ureteral catheter which is inserted into the sacral canal through a No. 13-gauge spinal needle. The disadvantages of the needle technique are breakage of needles, intravenous injection, trauma, and subdural injection and infection. These disadvantages are obviated by the use of the catheter technique. The dangers of continuous caudal anesthesia by either technique are reviewed. Contraindications to its use in certain conditions complicating pregnancy are also mentioned.

WILLIAM BERMAN

Batterman, Robert C., and Himmelsbach, C. K.: *Demerol—A New Synthetic Analgesic*, J. A. M. A. 122: 222, 1943.

Demerol possesses three main actions: analgesia, spasmolysis, and sedation. It is as effective as morphine in producing analgesia. One hundred milligrams of

demerol is as effective as 10 mg. of morphine. Oral administration of demerol is less effective than parenteral administration. It causes marked relief of smooth muscle spasm. It has an antispasmodic effect on the smooth muscle of the bronchi. It does not have the same effect on diarrhea that opiates have. Demerol, as a basal anesthetic agent prolongs the anesthesia time of a given amount of nitrous-oxygen anesthesia. It has little or no effect on cough. There is no effect on the size of the pupil. There is less nausea and vomiting than with morphine.

The dosage varies from 50 to 200 mg. depending upon the desired effect. It does not affect the hemopoietic system, liver, or kidneys. The drug is rapidly destroyed by the liver. It produces an increased threshold to painful stimuli at the periphery. In addition to this, tolerance develops rapidly to the somnifacient action and to many of the side actions. Prolonged uses of demerol may lead to habituation, but it appears to possess a lesser liability than morphine. In order to avoid the dangers of habituation, physical dependence, and undue cerebral irritability, amounts greater than 150 mg. every 3 hours should not be given.

WILLIAM BERMAN

Rovenstine, E. A., M.D., and Batterman, R. C., M.D.: *The Utility of Demerol as a substitute for the Opiates in Preanesthetic Medication*, *Anesthesiology* 4: 126, 1943.

In 1939, Eisleb and Schuman introduced a new synthetic, phenyl-pipecridene derivative, Demerol, which was found to possess properties similar to those of atropine and morphine. More recently Batterman concluded that demerol could be used as a substitute for the opiates, particularly as a substitute for morphine in preanesthetic medication. Pharmacologically, demerol is unique in that it possesses both atropine and morphine-like actions.

The authors used demerol in 338 unselected surgical patients, ranging in ages from fifteen to eighty-nine, as a preanesthetic sedative. All types of surgical anesthesia—inhalation, spinal, local—were employed. A satisfactory preanesthetic state was recorded in approximately 80 per cent of this series and suggests that it may be used as a substitute for morphine or other opiates.

HARVEY B. MATTHEWS

Klein, Bert H., Major, M.C.: *Two Hundred Deliveries Under Low Spinal Anesthesia*, *J. Missouri M. A.* 40: 305, 1943.

Low spinal anesthesia using 50 mg. of novocain in 1 c.c. spinal fluid in the fourth lumbar interspace was used in 200 deliveries with very gratifying results. There were no maternal deaths and no fetal deaths attributable to the anesthetic. Labor was definitely shortened, averaging 6.2 hours for the series. The method does not offer complete painless labor as in the case of caudal, because low spinal anesthesia is not given as early and not by the fractional or continuous technique. However, the author claims that it is less difficult to administer, is more rapid in action and the number of failures greatly reduced. Furthermore, all obstetric maneuvers, such as forceps, rotation, version, or version and extraction are carried out much more easily under spinal anesthesia. There is complete relaxation. Delivery in most cases was accomplished by episiotomy and prophylactic forceps but a few were allowed to deliver spontaneously merely to show that it could be done without the use of abdominal muscles. Blood loss was less than with general anesthesia and post-partum complications are reduced to a minimum.

The author feels that in selected cases low spinal anesthesia is "definitely a method of choice."

HARVEY B. MATTHEWS

Small, Maurice J.: A Serious Complication of Caudal Anesthesia, J. A. M. A. 122: 671, 1943.

The author reports a case of a secundigravida who was given caudal anesthesia using the drip method modification of the Hingson-Edwards technique. After one hour's injection, the patient rather suddenly began to show signs of a high spinal anesthesia. The patient was given artificial respiration and the usual stimulative therapy. The baby was extracted with forceps since the patient was completely dilated and the head was on the floor of the perineum. When the patient recovered she had sensory anesthesia as high as the lower axillary line. Following this period of shock the patient made an uneventful recovery.

WILLIAM BERMAN

Amaral, C.: Local Anesthesia for Vaginal Hysterectomy, Ann. brasil de ginec. 8: 203-214, 1943.

At the University of Brazil, twelve vaginal hysterectomies were performed under local anesthesia. The women were from 40 to 70 years of age. There were no deaths and the anesthesia was successful in ten cases (83.3 per cent). Amaral discusses the anatomy and nerve supply of the area of operation and she also reviews the literature on the subject of local anesthesia for vaginal operations.

J. P. GREENHILL

### Extrauterine Pregnancy

Johns, Frank: Ectopic Pregnancy, Virginia M. Monthly 70: 407, 1943.

A series of 130 cases of ectopic pregnancy operated upon in a private hospital by a capable surgical staff is reported. It is estimated that the incidence of ectopic pregnancy is about 1 to every 300 intrauterine pregnancies admitted. It occurs most often in parous women between 23 and 35 years. The etiology is unknown. This series showed a very small incidence of tubal infection, diverticula, adhesions or other factors which might interfere with passage of the ovum. It is emphasized that prompt management of ectopics within a few hours after rupture, early transfusion and prompt surgery were responsible for the low mortality in this group. Only one of these patients died, that because of the inability to obtain blood transfusions. The author recommends simple excision of the affected tube and removal of large blood clots from the abdominal cavity. Appendectomy and removal of the opposite tube is only done upon specific indication. Liberal transfusions of whole blood are indicated.

WILLIAM BICKERS

Anderes, E., and Laszczower, M.: A New Method of Reinfusion of Blood From the Abdominal Cavity as Well as a Technique for Aspirating Fluids From Body Cavities, Schweiz. med. Wchnschr. 72: 933-936, 1942.

The authors present their arguments in favor of using the blood which is found in the abdominal cavity at the time of operation for ruptured ectopic pregnancy. They describe a new method of aspirating and reinfusing this blood into the patient. At the time of aspiration, the blood is filtered and led into a container without contact with the air. Two new instruments are described and illustrated which facilitate the process of aspiration and reinfusion of the blood.

J. P. GREENHILL

Afredo, J.: Hemo-Reinfusion in Cases of Ruptured Ectopic Pregnancy, Ann. brasil. de ginec. 13: 352-360, 1942.

The author reports 26 cases of ruptured ectopic pregnancy in which he reinfused the blood taken from the abdominal cavity. There was only one death in this series. In three of the women more than 1,000 c.c. of blood were injected.

J. P. GREENHILL

De Souza, O.: Ectopic Pregnancy at Term, Ann. brasil. de ginec. 14: 30-34, 1942.

A case of full-term ectopic pregnancy was reported by the author. The diagnosis in this case was verified by hysterosalpingography. The operation performed was uneventful.

J. P. GREENHILL

### Gynecology

Wood, Juan W., Bunster, Edwardo M., and Pacheco, Matilde V.: Concerning the Laboratory Aids and Diagnosis of Adnexal Peritoneal Tuberculosis, Obstet. y ginec. Latino-Americanas 1: 33-49, 1943.

The preoperative diagnosis of genital tuberculosis is still difficult to make. Exploratory laparotomy continues to be the most certain method. The authors decided that since in adnexal tuberculosis, involvement of the uterus is secondary due to the downward passage of the disease into the uterus, they could make a diagnosis of pelvic tuberculosis by studying the endometrium. They therefore used the Randall curette and performed endometrial biopsies during the premenstrual phase in the hope of finding tubercle bacilli in the functional layer. They were able to make a correct diagnosis in 85 per cent of the cases investigated; hence this is the procedure of choice.

The authors also studied the cervical and vaginal discharges and found tubercle bacilli in only 37.5 per cent of the cases where smears were made; in 41.6 per cent where culture methods were employed and in 55.5 per cent where they resorted to inoculation into animals. In two cases of ascites the material obtained by pelvic puncture yielded tubercle bacilli. The Velez blood index gave 77.7 per cent positive results. The blood sedimentation rate was of no help in the diagnosis of pelvic tuberculosis.

J. P. GREENHILL

Lyon, Robert A.: Evaluation of Dysmenorrhea by Basal Body Temperature, Surg., Gynec. and Obst. 76: 729, 1943.

Studies of thirty dysmenorrheic women, including 127 cycles have led the author to conclude that there is a correlation between temperature rise and cramps. This is not conclusively proved by the graph shown, nor is a statistical analysis of the figures given. It is stated that anovulation is neither associated with dysmenorrhea, nor with temperature rise.

LT. L. M. HELLMAN, M.C., U.S.N.R.

Langley, G. F.: Primary Echinococcal Cyst of the Uterus, Brit. J. Surg. 30: 278, 1943.

The extreme rarity of echinococcal cyst of the uterus warrants mention of this case report. The patient, an unmarried female, 31 years of age, had had an intracranial hydatid cyst removed in 1923, resulting in papilledema and optic atrophy

rendering the patient blind during these 17 intervening years. The cystic pelvic mass incarcerated in the pelvis was removed by laparotomy and proved to be an echinococcal cyst of the uterus. There were no pelvic nor abdominal implants. After a very stormy convalescence, with numerous complications including right nephrectomy for extensive hydronephrosis (the right ureter had been cut and unsuccessfully anastomosed during original operation) the patient finally recovered (after 6 months) and is now able to carry on her work in an institution for the blind (3/2/43).

There is appended 6 references, all the available literature on the occurrence of echinococcal cyst of the uterus.

HARVEY B. MATTHEWS

Ahumada, J. C., and Sammartino, R.: *Endometriosis of the Vulva, Following Removal of Bartholin Glands*, *Rev. méd. Latino-Americana* 27: 93, 1942.

Endometriosis of the vulva and of the perineum is rare; nine cases of the former and 11 of the latter have been reported in the world literature, two with involvement of both areas and two situated in the pubis. The authors present an additional case in a single woman, aged 26, who was operated upon nine years after a left Bartholinitis, and a cyst, the size of a walnut, was removed. In the operative scar the patient had pain at the menstrual period and a painful tumor, walnut-sized, appeared. This opened spontaneously and later was removed, showing, on histologic study, endometriosis.

The authors review the literature and speculate on the origin of the lesion. They conclude from a study of various cases reported that the lesion is produced by embryonal rests, by production of endometrial metastases following the blood vessels and lymphatics, or by an autonomous growth of areas of tissue which still retain the capacity of differentiation of embryonic tissue.

J. P. GREENHILL

### Gynecologic Operations

Brunner, C.: *Prophylaxis of Postoperative Cystitis*, *Schweiz. med. Wchnschr.* 73: 173-175, 1943.

As a prophylactic measure against postoperative cystitis, the author recommends that a retention catheter be inserted immediately after operation and left in the bladder for seven days. During this time the patient should receive a sulfa drug. A specimen of the urine is taken at the time the catheter is inserted and again on the fourth and seventh days. These specimens are cultured. A control specimen is again taken four to six weeks after the patient leaves the hospital. In a series of 23 cases where this procedure was carried out, there was not a single instance of cystitis.

J. P. GREENHILL

Dutra, L. H.: *Menstruation-Preserving Hysterectomy*, *Ann. brasil de ginec.* 15: 351-394, 1943.

Dutra (Brazil) describes the technique of the type of hysterectomy he has devised. By means of a U-shaped incision most of the uterus is removed but enough endometrial tissue is left behind to permit menstruation. The author believes there is a functional synergism between the uterus and ovaries and unless this synergistic relationship is maintained, harm will result. In performing his operation he controls bleeding by using a rubber catheter to constrict the uterine arteries and ovarian pedicles. In a follow-up of the patients, the author found that most of them men-

struated, and that they had no symptoms of ovarian deficiency. Pelvic examination failed to reveal cystic degeneration of the ovaries. In some cases, hysterosalpingograms were made to determine the size of the uterine cavity which was left.

J. P. GREENHILL

Palazzo, Orestes R.: Chronic Cervicitis: 4,000 Cases Treated With Diathermy Coagulation, Arch. Clin. obst. y ginec. "Eliseo Cantón" 2: 118-123, 1943.

On a basis of 20 years' experience in the treatment of chronic cervicitis with various methods the author concludes that diathermy coagulation is the most efficient and convenient method. It is applicable in all types of cases, eliminates the necessity for amputation of the cervix, and cures not only the erosion but corrects deformities caused by labor. It is not used in the presence of acute or subacute inflammatory processes, until six months after disappearance of symptoms. Determination of the sedimentation rate is recommended in patients with a history of adnexal inflammation. The treatment is best administered on the second or third day after menstruation, to avoid metrorrhagia which may result when the congestion caused by the diathermy is added to menstrual congestion. Caution should be exercised not to produce stenosis. This is not probable in most cases, because usually the external orifice presents a wide opening. With retraction of the edges, the cervical orifice regains its normal shape and size. The proper effect depends on knowing how to regulate the depth to which the coagulating action is carried, which will be directly proportional to the intensity of the current and the time of application.

Palazzo recommends the spherical monopolar electrode as the most effective, harmless and economic method of using the diathermy coagulating current.

J. P. GREENHILL

Leon, Juan, and Leon, Carlos T.: Dermoid Cysts of the Ovary: Radiologic Diagnosis in Pregnant and Nonpregnant Women, Arch. Clin. obst. y ginec. "Eliseo Cantón" 2: 93-118, 1943.

The authors emphasize the importance of roentgenographic examination of dermoid cysts, especially during pregnancy in differentiation from pedunculated fibromas of the uterus. The outstanding radiologic findings are shadows corresponding to bony parts and teeth, delineation of the capsule of the tumor, and marked transparency of the tumor image (Odqvist and Laurell sign).

Two cases are reported, one in a nonpregnant patient, and the other in a pregnant woman. Preoperative radiologic study was correlated with radiologic and pathologic study of the tumors after their removal.

Despite the high incidence of sterility in women with dermoid cysts (22.4 per cent according to Meyer) there are numerous observations of such tumors found during the puerperal state. Most of the reports, however, consist of single cases. No precise statistics are available because there are usually no symptoms. Nevertheless, their diagnosis is often facilitated by pregnancy which makes them more accessible to palpation, and sometimes their size is increased during gestation because of edema or hemorrhage. The authors report five cases of dermoid cysts and pregnancy from the records of the Eliseo Cantón clinic.

J. P. GREENHILL

# Items

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## Urology Award

The American Urological Association offers an annual award not to exceed \$500 for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, June 19 to 22, 1944, Hotel Jefferson, St. Louis, Missouri.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1944.

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## American Board of Obstetrics and Gynecology, Inc.

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pa., by the entire Board from Wednesday, June 7, through Tuesday, June 13, 1944. The Hotel William Penn in Pittsburgh will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 15, 1944.

The Pittsburgh Obstetrical and Gynecological Society will hold an informal subscription dinner meeting at the Hotel William Penn, on Saturday evening, June 10, 1944, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary, at 121 University Place, Pittsburgh 13, Pa. An interesting program is being provided.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1945 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.

February 18, 1944.

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## Original Communications

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### THE EFFECT OF THE INTERVAL BETWEEN BIRTHS ON MATERNAL AND FETAL OUTLOOK\*

NICHOLSON J. EASTMAN, M.D., BALTIMORE, MD.

*(From the Department of Obstetrics, Johns Hopkins University and Hospital)*

IN THE year 1925, there appeared a monograph which has probably had more influence on the pattern of childbearing in this country than any half dozen other publications. Its title was "Causal Factors in Infant Mortality, A Statistical Study Based on Investigations in Eight Cities"; its author was Robert Morse Woodbury, Ph.D., then director of statistical research in the Children's Bureau, U. S. Department of Labor. Dr. Woodbury's study is an extremely meticulous and exhaustive analysis of the more important causal agents in infant mortality; and among other factors especial attention is given to the role played by the interval of time since the preceding birth. After a careful survey of many aspects of the problem the conclusion is reached that "the infants born after short intervals had a markedly high rate of mortality from all causes. Evidently some factor that is intimately connected with the short interval—perhaps through the influence of frequent births upon the mother's health—affected adversely the chances of life of the infants who followed closely after preceding births." The specific infant mortality figures for the first year of life reported per 1,000 were as follows: for those in whom the interval

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\*Read (by invitation) at a meeting of the Chicago Gynecological Society, November 19, 1943.

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."



since the preceding birth was one year, 146.7; for those in whom the interval was two years, 98.6; for the three-year-interval group, 86.5; and for those in whom the interval was four years and more, 84.9. The corresponding figures for neonatal deaths were: 51.2; 37.3; 36.7 and 38.1. Stillbirth data (p. 170) followed a similar trend. In round numbers, then, it was found that infants born after an interval of but one year following a preceding birth, faced a mortality which was one and a half times that met by infants born after intervals of two years or more. The lowest mortality for the entire first year of life was enjoyed by infants born four or more years after a previous childbirth.

Dr. Woodbury's monograph is a reserved and scholarly study, largely objective in character; and it contains no suggestion whatsoever as to what might be done to reduce infant mortality in the short interval groups. But those interested in the furtherance of birth control were quick to see a remedy. Certainly, they reasoned, if conception could be prevented in women during the first year or two after childbirth, the high mortality associated with the short interval could be prevented. And forthwith the Woodbury study became one of the cornerstones of the birth control movement and has remained so ever since. Upon it, indeed, is based the entire rationale, from a medical viewpoint, of so-called "child spacing," a term which has come to be a sort of euphemism for contraception in general. Moreover, information about this presumably high infant mortality associated with short interval births has been given such wide circulation that it is frequently stressed in our lay periodicals—always with the implication that it is a generally accepted truth, almost one of the axioms of childbearing. For instance, in the September, 1943 issue of *The Reader's Digest* an article appeared entitled "Questions on Childbirth." It starts with the challenging query, "How much do you know about the latest scientific findings as to childbirth?" Then follow a series of statements which the reader is supposed to check as "true" or "false." These comprise, in main, elementary and commonly accepted obstetric facts. Along with these, item No. 23 reads as follows: "Babies born at yearly intervals to a mother are as likely to live as if there were periods of several years between them." The answer given is: "False. Where the interval between the births of two babies is less than two years, the infant mortality rate is one and a half times as high as if the children were spaced." A footnote states, "The American Medical Association has verified the facts in this article." Here then, again, are Dr. Woodbury's figures, having reached (after approval by the American Medical Association) the *Reader's Digest* with its millions of readers.

Because of the wide influence which the Woodbury monograph has exerted, it would seem appropriate to review that portion of it which deals with the short interval problem. This comprises an analysis of

8,196 births in Baltimore, all occurring between January 1, and December 31, 1915, that is, twenty-eight years ago. In view of the many lifesaving advances which have been made both in pediatrics and obstetrics over this period, it would seem permissible to question whether conclusions drawn from births occurring in 1915 are valid today. The only other study of this type which we have been able to discover is one by Elizabeth Hughes, carried out in Gary, Indiana, in 1916. Analyzing 1,135 births (other than first births) she found that the infant mortality, under one year, was 169.1 per 1,000 live births when the interval was less than 15 months, but fell to 102.8 when the interval exceeded two years.

It is the purpose of the present communication to report an investigation based on modern material, of the effect of the interval between births on maternal and fetal outlook. The study consists of two parts. In the first, the case histories of 5,158 obstetric patients are reviewed, in all of which the interval between the previous viable delivery and the termination of the present pregnancy was accurately known and recorded on statistical punch cards. Since this portion of the investigation is based on direct knowledge of the interval between births, it may be regarded as a "direct study" of the effect of certain intervals on various maternal and fetal phenomena. In the second part of the investigation, 33,087 obstetric cases are reviewed in which the interval between births was not specifically recorded on punch cards. However, the age and parity of the patients were so recorded and by correlating these two factors (particularly great parity in younger age groups) it was possible to draw conclusions indirectly about the effect of rapid childbearing (and hence short average intervals) on maternal and fetal prognosis. This part of the investigation will be referred to as the "indirect study."

### Direct Study

The 5,158 patients in the direct study were all delivered at the Johns Hopkins Hospital between September 1, 1936 and June 30, 1943. The series was a consecutive one with the following exceptions: (1) All primiparas, of course, were excluded as were those cases in which the only previous pregnancy had terminated in an abortion. In other words, there had been in every case a previous viable delivery. (2) All cases, relatively few in number, were omitted in which the pregnancy subsequent to a viable delivery terminated in a well-attested criminal abortion. The latter group of cases would obviously vitiate any conclusions drawn in regard to the effect of the preceding interval on the *spontaneous* outcome of a subsequent pregnancy.

The distribution of the 5,158 cases according to the interval since the last viable delivery is shown in Table I, while in Table II, the various interval groups are subdivided according to race and class. It is ap-

parent from the latter table that the pattern of childbearing, that is, the extent to which births are spaced, differs considerably in the three racial and economic groups. In more than a third of the colored patients the interval since the last viable delivery was less than two years; about a quarter of the white ward cases fell into this brief interval group but only one-sixth of the private patients. In about one-half of the private patients the interval was between 25 and 48 months, suggesting that intentional child spacing is the rule among this class. It should be noted in particular that the brief interval groups are disproportionately weighted with colored patients while the longer interval groups contain relatively fewer of them. Since it is well known that both stillbirth and neonatal mortality, as well as maternal mortality, are higher in the colored race, the odds in this series are weighted somewhat against the brief interval groups.

Because the number of cases in some of the longer interval groups are too small to permit of valid statistical analysis and also for the sake of clarity, the cases have been classified in four main interval groups as shown in Table III, and henceforth, will be considered according to those categories. However, because of the great importance of the 'Very Brief' interval group for our purpose, it has been kept intact despite its

TABLE I. DISTRIBUTION OF 5,158 OBSTETRIC CASES ACCORDING TO INTERVAL SINCE LAST VIABLE DELIVERY

INTERVAL	CASES	PER CENT OF TOTAL
Less than 12 months	115	2.2
Between 13 and 24 months	1,347	26.1
Between 25 and 36 months	1,416	27.5
Between 37 and 48 months	775	15.0
Between 49 and 60 months	465	9.0
Between 61 and 72 months	284	5.5
Between 73 and 84 months	194	3.8
Between 85 and 96 months	129	2.5
Between 97 and 108 months	98	1.9
Over 9 years	335	6.5
	5,158	100.0

TABLE II. DISTRIBUTION OF 5,158 OBSTETRIC CASES ACCORDING TO INTERVAL SINCE LAST VIABLE DELIVERY AND ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE WARD		COLORED WARD		PRIVATE (WHITE)	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Less than 12 mo. (1st yr.)	31	1.4	74	3.3	10	1.3
13 to 24 mo. (2nd yr.)	521	24.2	714	31.6	112	15.0
25 to 36 mo. (3rd yr.)	524	24.4	702	31.0	190	25.5
37 to 48 mo. (4th yr.)	326	15.2	272	12.0	177	23.8
49 to 60 mo. (5th yr.)	223	10.4	154	6.8	88	11.8
61 to 72 mo. (6th yr.)	170	7.9	63	2.8	51	6.8
73 to 84 mo. (7th yr.)	109	5.1	60	2.6	25	3.4
85 to 96 mo. (8th yr.)	61	2.8	47	2.1	21	2.8
97 to 108 mo. (9th yr.)	52	2.4	32	1.4	14	1.9
Over 9 years (10th yr.)	134	6.2	144	6.4	57	7.7
Total	2,151	100.0	2,262	100.0	745	100.0

small size. Fig. 1 shows the percentage composition of these four interval groups according to race and class, and directs attention again to the decreasing incidence of colored cases as the interval lengthens and the increasing frequency of white cases.

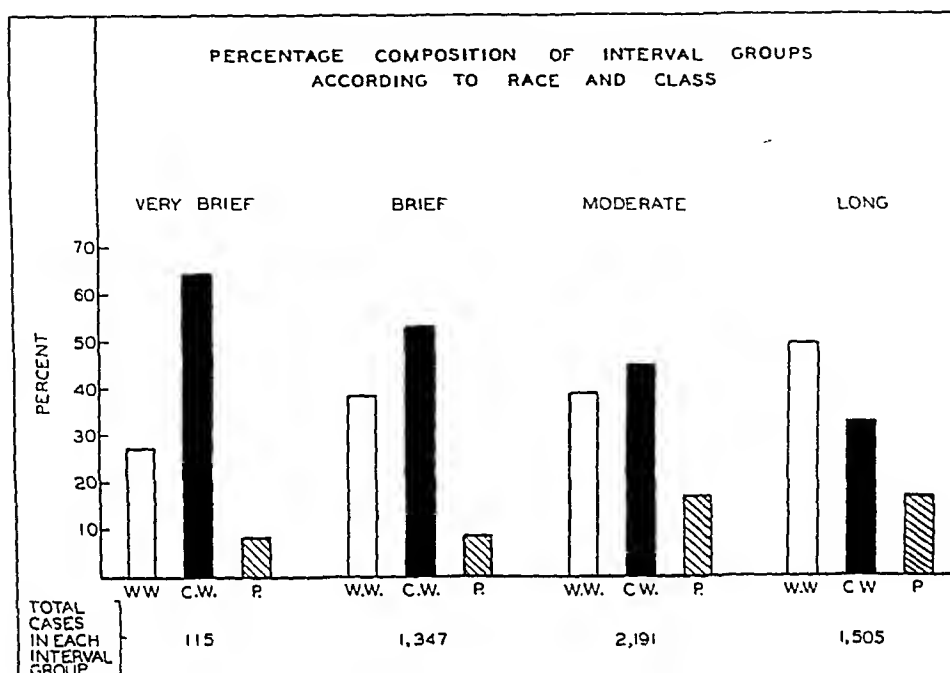


Fig. 1.—Percentage composition of the four main interval groups according to race and class. W.W. = White Ward; C.W. = Colored Ward; P. = Private.

TABLE III. DISTRIBUTION OF 5,158 OBSTETRIC CASES IN FOUR MAIN GROUPS ACCORDING TO WHETHER INTERVAL SINCE LAST VIABLE DELIVERY WAS VERY BRIEF, BRIEF, MODERATE OR LONG

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	PER CENT OF TOTAL
Very Brief—Less than 12 months	115	2.2
Brief—13 to 24 months	1,347	26.1
Moderate—25 to 48 months	2,191	42.5
Long—More than 48 months	1,505	29.2
Total	5,158	100.0

Having classified our 5,158 multiparas into four main groups according to the interval since the last viable delivery, it might seem that our only remaining task would be to analyze the percentage of infant deaths, the percentage of maternal complications and the maternal mortality in each group, and therewith the answer to our question would be at hand. Actually, the problem is much more difficult than this since the interval between births is closely correlated with certain other factors which are known to exert a most important influence on maternal and fetal outlook. Thus, the outcome for both mother and child is related to age and parity; and, naturally, women in the longer interval groups are older, as a rule, than those in the briefer interval brackets. The relative num-

ber of colored patients in each group, as already mentioned, is another possible source of error. All these complicating findings will have to be carefully weighed and, if possible, controlled in evaluating the data.

But perhaps the greatest potential source of error in this study is a certain *time element* involved in the 'Very Brief' interval group; and unless this is thoroughly understood, any conclusions drawn from this category will be totally invalid. It will be recalled that it was in this group that Woodbury found such a very high infant mortality. As shown diagrammatically in Fig. 2, if a woman is to give birth to a full-term infant within twelve months after a previous delivery, conception must take place before the end of the third month, because obviously

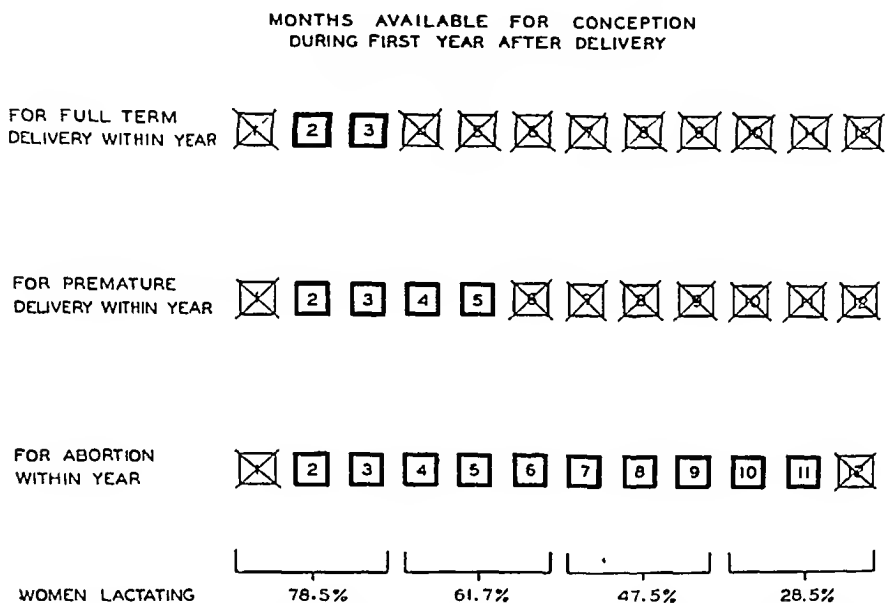


Fig. 2.—Showing that if a full-term infant is to be born within one year after a previous delivery, only two months are available for conception; but if a premature infant is to be born within the same period, four months are available; while for an abortion to take place within this interval ten months are available for conception. Below is shown the percentage of women who are lactating at various intervals after delivery and who are therefore relatively infertile.

nine calendar months are required for the development of a full-term baby. Accordingly, if we assume that ovulation does not occur within the first thirty days after delivery and in any event, that conceptions during this first month must be exceedingly rare, there are only two months in which conception can occur if a full-term infant is to be born within a span of twelve months following a previous delivery. On the other hand, in the case of premature infants, there are four months available since less time is required for the development of a premature baby. In the case of abortions, there are ten months in which a woman can conceive and abort within the year; it is, indeed, easily possible for a woman to have two abortions within twelve months after a previous delivery. Therefore, in any series of pregnancies which terminate within a year after a previous delivery, the incidence of premature deliveries

is bound to be high, possibly twice as high as usual, since there are four months available for conception and premature delivery and only two months if the subsequent delivery is to be full term. By the same token, we should expect that the relative incidence of abortion in this group would be exceedingly high. But we have reckoned thus far without considering the factor of lactation which, of course, suppresses ovulation and tends to produce temporary sterility. As the figures on the lower part of Fig. 2 indicate, fewer women are lactating in the fourth and fifth months than in the second and third, and therefore, a larger percentage are presumably fertile during the fourth and fifth months. But for a woman to conceive during these months and give birth within a year after the previous delivery, it is obviously obligatory that she go into labor prematurely. This would swell still further the incidence of premature delivery in the 'Very Brief' interval group—perhaps to two and a half or three times its normal frequency. An increase in the incidence of prematurity of this magnitude is, therefore, to be expected in this group as the inevitable result of the time element, and when confined to this magnitude, is in no way indicative of any inherent tendency of these women to have premature babies.

TABLE IV. INCIDENCE OF ABORTION IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	ABORTION	PER CENT
Very Brief—Less than 12 months	115	47	40.9*
Brief—13 to 24 months	1,347	122	9.1
Moderate—25 to 48 months	2,191	135	6.2
Long—More than 48 months	1,505	139	9.2

\*Figure not a valid index as shown in Fig. 2 and explained in text.

As was anticipated the incidence of abortion in the 'Very Brief' group (Table IV) was exceedingly high, namely 40.9 per cent. The frequency of the condition in the 'Brief' and 'Long' groups, 9.3 per cent, as compared with the incidence in the 'Moderate' group, 6.7 per cent, represents a difference which is statistically significant; but the likelihood that many of these abortions were artificially produced vitiates any conclusions which might be drawn from this complication.

TABLE V. INCIDENCE OF PREMATURE DELIVERY IN THE FOUR MAIN INTERVAL GROUPS ACCORDING TO RACE

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	WHITE			COLORED		
		PREMA-TURE	PER CENT		CASES	PREMA-TURE	PER CENT
Very Brief—Less than 12 months	41	8	19.5*	} 5.6	74	30	40.5*
Brief—13 to 24 months	633	30	4.7		714	65	9.1
Moderate—25 to 48 months	1,217	59	4.8		974	76	7.8
Long—More than 48 months	1,005	49	4.9		500	48	9.6

\*Figure not a valid index as shown in Fig. 2 and explained in text.

Table V shows the incidence of prematurity in the four main interval groups according to race. (For the purpose of this study a premature infant is considered as one weighing less than 2,500 grams but more than 1,499 grams). This table brings out several facts: (1) The incidence of prematurity in the colored race was almost twice that in the white so that in this condition, it is obviously desirable to consider the two races separately. (2) The incidence of prematurity among white patients in the 'Very Brief' group was 4.1 times that met in the longer interval groups; and in the colored 4.7 times. Since we have estimated that the "time element" alone could account for an increased incidence of prematurity in this group of but two and a half to three times, there is a slight suggestion here that, superimposed on the time element, another intrinsic factor in these very early conceptions may be at work making for premature delivery. Additional evidence along these lines will be advanced presently. (3) In the white race the incidence of prematurity in the 'Brief,' 'Moderate' and 'Long' groups is almost identical. This means that in the white race, at least, conceptions which take place six or more months after a previous delivery stand no greater chance of terminating in premature births than those conceived after longer intervals. The same may also be true of the colored since the difference between our figures for the three groups, 9.1, 7.8 and 9.6 per cent is not statistically significant and may be due to chance. (4) If now the 'Very Brief' and 'Brief' groups are combined (thus eliminating for all practical purpose the "time element" in the 'Very Brief' group) it is apparent that the resultant percentage is higher for both races, than in the 'Brief' group taken alone. Now if, with the time element eliminated, the 'Very Brief' group had the same incidence of prematurity as the 'Brief' group, combining the two should not raise the percentage. Since it does so, we find here another suggestion that very early conceptions (before six months after a previous delivery) show a certain tendency to premature delivery.

Another suggestion that very early conceptions after a previous delivery show a greater incidence of premature birth may be adduced in another way. Consider those conceptions in this series which occurred in the fourth and fifth months. Of the 38 premature births in the 'Very Brief' interval group, it seems highly probable that at least 25 took place in these months. But, in addition, a certain number of conceptions occurred at this same period which went to term and were delivered in the first and second months of the second year. The exact number of these conceptions which terminated maturely we do not know, but we can estimate them as not more than one-sixth of the total full-term deliveries for the second year, namely 200, in round figures. This gives an incidence of prematurity for those pregnancies conceived in the fourth and fifth months post partum of 11.1 per cent, a figure which is definitely

higher than cited in Table V for the 'Brief,' 'Moderate' and 'Long' groups. Accordingly, we find suggestive evidence of three types pointing to a somewhat higher incidence of prematurity among pregnancies conceived within five months after a previous delivery. But for pregnancies conceived later than this, let us say, after the sixth month, we find no such evidence.

Tables VI, VII and VIII show the stillbirth, neonatal and total infant mortality rates in the four main interval groups. The high fetal mortality in the 'Very Brief' groups becomes understandable when it is noted that four of the five stillbirths and nine of the eleven neonatal deaths occurred in premature infants; in other words, we see here the practical effect of the "time element" expressed in terms of infant mortality. It seems probable that the same factor may have played a role in the high mortality reported in the Woodbury study for the same group, since the incidence of prematurity in the "one year interval group" of that investigation was 77 per cent higher than in the "two year interval group" (Woodbury, Table 48, page 64). In our series the stillbirth rate was identical in the 'Brief,' 'Moderate' and 'Long' interval groups, while the neonatal death rate tended to rise slightly as the interval increased.

TABLE VI. INCIDENCE OF STILLBIRTH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	STILLBIRTHS	PER CENT
Very Brief—Less than 12 months	71	5*	7.0†
Brief—13 to 24 months	1,245	36	2.9
Moderate—25 to 48 months	2,109	63	3.0
Long—More than 48 months	1,404	41	2.9

\*Four of these five stillbirths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE VII. INCIDENCE OF NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	NEONATAL DEATHS	PER CENT
Very Brief—Less than 12 months	71	11*	15.5†
Brief—13 to 24 months	1,245	19	1.5
Moderate—25 to 48 months	2,109	46	2.2
Long—More than 48 months	1,404	37	2.6

\*Nine of these eleven neonatal deaths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE VIII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	71	16	22.5* }
Brief—13 to 24 months	1,245	55	4.4 }
Moderate—25 to 48 months	2,109	109	5.2 }
Long—More than 48 months	1,404	78	5.6 }

\*Figure not a valid index as shown in Fig. 2 and explained in text.



Tables IX to XV represent a breakdown of the infant mortality figures just discussed in an effort to correct for prematurity, parity and race. Each table shows a similar pattern. The lowest mortality is met in the 'Brief' group with a slightly increasing rate in the longer interval groups, except in Table XV in which the small number of cases in the 'Long' group entails a large sampling error. As we have already

TABLE IX.—INCIDENCE AMONG MATURE INFANTS ONLY OF STILLBIRTH AND NEONATAL DEATH, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	30	3	10.0
Brief—13 to 24 months	1,146	29	2.5
Moderate—25 to 48 months	1,966	57	2.9
Long—More than 48 months	1,302	41	3.1

TABLE X. INCIDENCE AMONG PREMATURE INFANTS ONLY OF STILLBIRTH AND NEONATAL DEATH, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	41	13	31.7
Brief—13 to 24 months	99	26	26.3
Moderate—25 to 48 months	143	52	36.4
Long—More than 48 months	102	37	36.3

TABLE XI. INCIDENCE AMONG PARA II ONLY OF STILLBIRTH AND NEONATAL DEATH IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	36	9*	25.0†
Brief—13 to 24 months	520	17	3.3
Moderate—25 to 48 months	816	28	3.4
Long—More than 48 months	497	19	3.8

\*Six of these nine deaths occurred in premature infants.

†Figure not a valid index as shown in Fig. 2 and explained in text.

TABLE XII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *White Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	23	5	21.7
Brief—13 to 24 months	574	20	3.5
Moderate—25 to 48 months	1,161	46	4.0
Long—More than 48 months	940	42	4.5

TABLE XIII. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Colored Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	48	11	22.9
Brief—13 to 24 months	671	35	5.2
Moderate—25 to 48 months	948	63	6.6
Long—More than 48 months	464	36	7.8

stressed, it is our opinion that the high mortality in the 'Very Brief' interval group is largely the result of the high percentages of prematurity in this group due to the inescapable "time element."

Turning now to the effect of the interval between births on maternal outlook, Table XVI shows that there is no significant difference between the incidence of anemia in the 'Brief,' 'Moderate' and 'Long' groups. The figures for the 'Very Brief' group are too small to warrant conclusions.

TABLE XIV. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Para II, White Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very brief—Less than 12 months	13	2	15.4
Brief—13 to 24 months	286	5	1.7
Moderate—25 to 48 months	551	11	2.0
Long—More than 48 months	358	9	2.5

TABLE XV. INCIDENCE OF STILLBIRTH AND NEONATAL DEATH, *Para II, Colored Only*, IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	TOTAL INFANT MORTALITY	PER CENT
Very Brief—Less than 12 months	23	7	30.4
Brief—13 to 24 months	234	12	5.1
Moderate—25 to 48 months	265	17	6.4
Long—More than 48 months	122	5	4.1

TABLE XVI. INCIDENCE OF MATERNAL ANEMIA\* DURING PREGNANCY IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	WHITE ANEMIA	PER CENT	CASES	COLORED ANEMIA	PER CENT
Very Brief—Less than 12 months	16	4	25.0	29	10	34.5
Brief—13 to 24 months	438	55	12.6	520	144	27.7
Moderate—25 to 48 months	781	102	13.1	742	236	31.8
Long—More than 48 months	675	88	13.0	393	94	23.9
Total	1,910	249	13.0	1,684	484	28.7

\*By anemia is meant less than 10 grams of hemoglobin per 100 c.c. of blood, i.e., less than 70 per cent.

TABLE XVII. INCIDENCE OF TOXEMIA OF PREGNANCY (ALL TYPES) IN THE FOUR MAIN INTERVAL GROUPS, ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE WARD	WHITE WARD	WHITE WARD	COLORED WARD	COLORED WARD	COLORED WARD	PRIVATE	PRIVATE	PRIVATE
	CASES	TOX-EMIA	PER CENT	CASES	TOX-EMIA	PER CENT	CASES	TOX-EMIA	PER CENT
Very Brief									
Less than 12 months	19	4	21.1	45	7	15.6	4	0	0.0
Brief									
13 to 24 months	465	55	11.8	655	144	22.0	105	3	2.9
Moderate									
25 to 48 months	794	137	17.3	918	230	25.1	344	19	5.5
Long									
More than 48 months	688	139	20.2	453	140	30.9	235	19	8.1
Total	1,966	335	17.0	2,071	521	25.2	688	41	6.0

One of the most striking effects of the interval between births encountered in this study is in the incidence of toxemia of pregnancy (pre-eclampsia, eclampsia and chronic hypertensive vascular disease combined). It seems clear from Table XVII that in each of the three racial and economic groups considered, the incidence of toxemia increases decidedly as the interval increases. (The high figures for toxemia in both the white and colored ward groups is due to the fact that the ward service is a consultation center for nineteen prenatal clinics scattered throughout Maryland. Our ward population is, therefore, not a representative cross section of the population at large either white or colored). Likewise, as shown in Table XVIII, the incidence of "repeat toxemias" increases with prolongation of the interval. This latter fact has already been demonstrated by Chesley and his associates.

TABLE XVIII. INCIDENCE OF "REPEAT" TOXEMIA IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES TOXEMIA PREVIOUS PREGNANCY	TOXEMIA SUBSEQUENT PREGNANCY	PER CENT
Very Brief—Less than 12 months	15	7	46.7
Brief—13 to 24 months	264	107	40.5
Moderate—25 to 48 months	431	191	44.3
Long—More than 48 months	190	98	51.6
Total	900	403	44.8

There was no significant difference between the incidence of post-partum hemorrhage or of puerperal fever in the four main interval groups. (Tables XIX and XX).

TABLE XIX. INCIDENCE OF POST-PARTUM HEMORRHAGE\* IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	CASES	HEMORRHAGE	PER CENT
Very Brief—Less than 12 months	68	0	0.0
Brief—13 to 24 months	1,225	30	2.4
Moderate—25 to 48 months	2,056	88	4.3
Long—More than 48 months	1,376	47	3.4
Total	4,725	165	3.5

\*By post-partum hemorrhage is meant blood loss of 600 c.c. or more.

TABLE XX. INCIDENCE OF PUERPERAL FEVER IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIABLE DELIVERY	WHITE			COLORED		
	CASES	FEVER	PER CENT	CASES	FEVER	PER CENT
Very Brief Less than 12 months	23	2	8.7	45	10	22.2
Brief 13 to 24 months	570	48	8.4	655	147	22.4
Moderate 25 to 48 months	1,138	114	10.0	918	196	21.3
Long More than 48 months	923	90	9.7	453	93	20.5
Total	2,654	254	9.6	2,071	446	21.5

The ability to nurse the baby without supplementary feeding, is usually taken as indicative of a healthy maternal state. Table XXI shows that, with the exception of the 'Very Brief' group, the incidence of breast feeding only was the same in all the interval groups. The high percentage of premature babies in the 'Very Brief' group accounts presumably for the high frequency of artificial feeding in this category. The mean birth weight of the mature babies and their mean weight gain in the hospital, in respect to their birth weight, showed no substantial differences. (Table XXII).

TABLE XXI. INCIDENCE OF BREAST FEEDING ONLY IN THE FOUR MAIN INTERVAL GROUPS ACCORDING TO RACE AND CLASS

INTERVAL SINCE LAST VIALE DELIVERY	WHITE WARD			COLORED WARD			PRIVATE		
	CASES	B.F.	PER CENT	CASES	B.F.	PER CENT	CASES	B.F.	PER CENT
Very Brief									
Less than 12 months	19	7	36.8	48	13	27.1	4	0	0.0
Brief									
13 to 24 months	469	326	69.5	671	447	66.6	105	55	52.4
Moderate									
25 to 48 months	812	516	63.5	948	679	71.6	349	183	52.4
Long									
More than 48 months	702	462	65.8	464	290	62.5	238	104	43.7
Total	2,002	1,311	65.5	2,131	1,429	67.1	696	342	49.1

TABLE XXII. MEAN BIRTH WEIGHT OF MATURE INFANTS (2,500 GRAMS AND OVER) AND MEAN WEIGHT GAIN IN HOSPITAL, IN RESPECT TO BIRTH WEIGHT, OF BREAST-FED MATURE INFANTS, IN THREE MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	MEAN BIRTH WEIGHT	MEAN WEIGHT GAIN
Very Brief—Less than 12 months	1,316	3,355 grams	11.8 grams
Brief—13 to 24 months			
Moderate—25 to 48 months	2,109	3,411 grams	31.7 grams
Long—More than 48 months	1,404	3,407 grams	29.5 grams
Total	4,829	3,395 grams	19.5 grams

Finally, in the direct study, the maternal mortality in the four main interval groups was essentially the same. (Table XXIII).

TABLE XXIII. MATERNAL MORTALITY IN THE FOUR MAIN INTERVAL GROUPS

INTERVAL SINCE LAST VIALE DELIVERY	CASES	DEATHS	PER CENT
Very Brief—Less than 12 months	115	0	0.00
Brief—13 to 24 months	1,347	3	0.22
Moderate—25 to 48 months	2,191	7	0.32
Long—More than 48 months	1,505	6	0.40
Total	5,158	16	0.31

### Indirect Study

The rationale of the indirect study is as follows: It is well known that fetal mortality varies with both parity and age, as shown in Figs. 3 and 4. Now if, instead of plotting total fetal mortality by age, as done in Fig. 4, we plot only the fetal mortality of para ii by age, we do

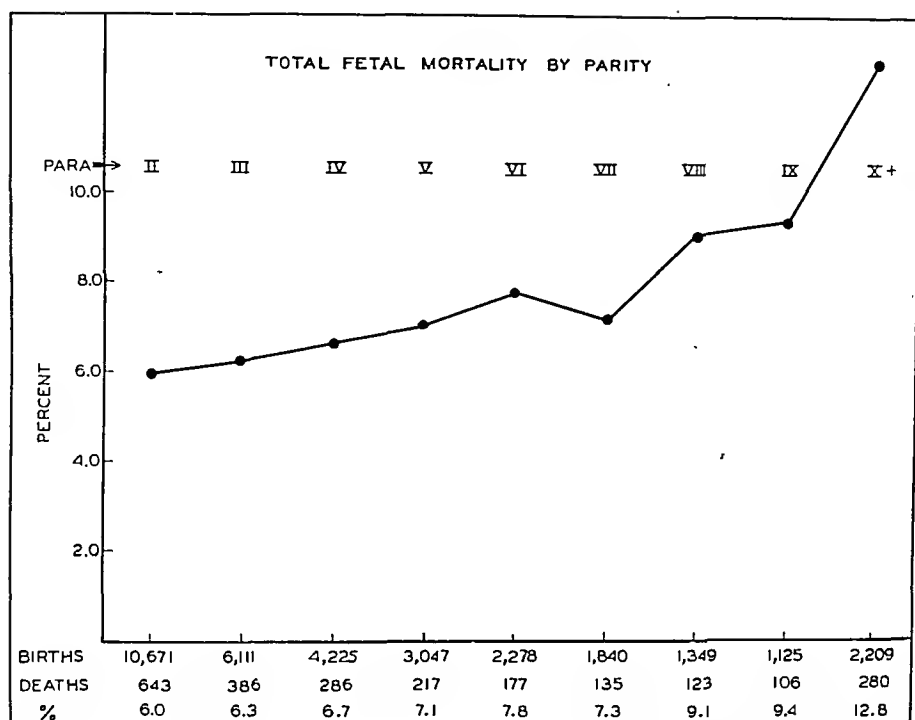


Fig. 3.—The upward trend of fetal mortality (stillbirth and neonatal) with increasing parity. (Primipara omitted).

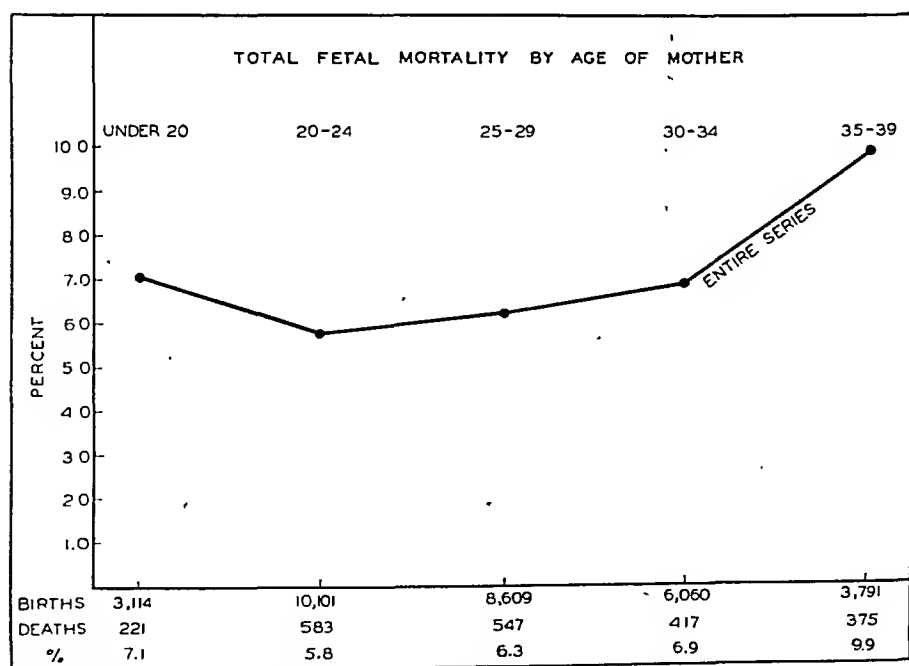


Fig. 4.—The curve of fetal mortality (stillbirth and neonatal) according to age of mother.

away with variations caused by parity and can ascertain fetal mortality in any age group in women of this particular parity. The resultant curve (marked para ii) is plotted in Fig. 5. From this we learn, for instance, that for para ii, ages 20 to 24, the fetal mortality is 5.5 per cent; and for para ii, ages 25 to 29, 5.1 per cent. Now let us superimpose on this graph the fetal mortality curve of para iv by age. Since women with a parity of iv have a higher fetal mortality than those with a parity of ii (as shown in Fig. 3), the curve of the para iv group will naturally fall at a somewhat higher level. However, provided there are no other factors at work affecting fetal mortality in one age group more than another, the two curves should be parallel. As shown in Fig. 5, these two curves do run approximately parallel in our series.

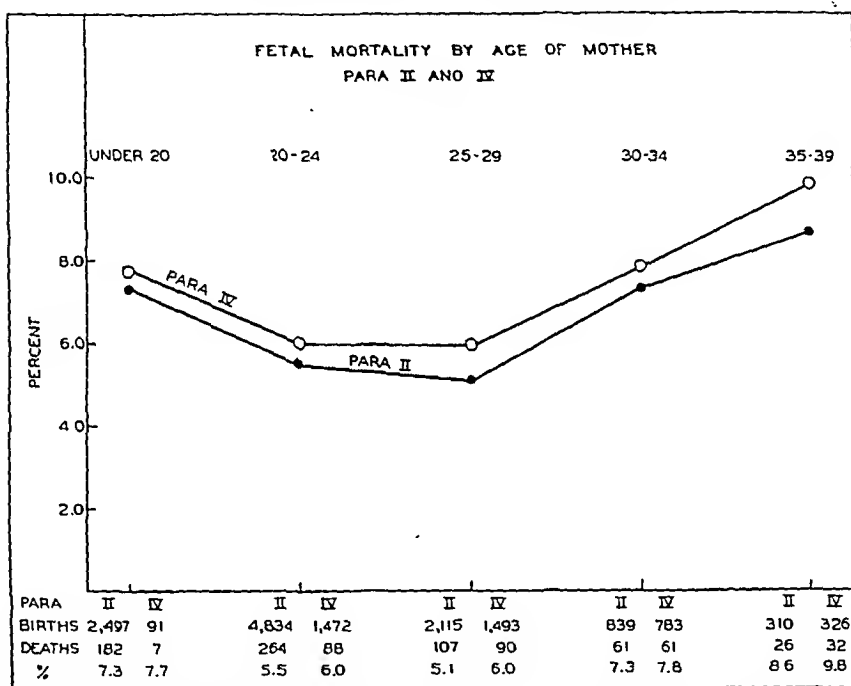


Fig. 5.—The curve of fetal mortality (stillbirth and neonatal) according to age of mother, para ii and para iv only.

Let us now consider the age groups (para ii and iv) ages 20 to 24. Obviously in any large aggregation of cases such as this, women who have had four babies before age 24 have had on the average a shorter interval between births than those who have had only two before age 24. We can conclude, then, indirectly that the para iv, ages 20 to 24 represent a shorter interval group than para ii, ages 20 to 24. Now if the shorter interval between births characteristic of the para iv, ages 20 to 24, exerted a deleterious effect on fetal mortality, it should cause a deviation upward of the mortality curve at this point. Actually no such deviation is encountered. Moreover, the graph shows that a woman who is giving birth to her fourth child between 20 and 24 experiences

no greater fetal mortality than the woman who is being delivered of her fourth infant between 25 and 29, although obviously in any large series the average interval between births in the latter age group would be greater.

If this type of analysis is pressed further and the mortality curve of para v is superimposed on that of para ii (Fig. 6), we find that the curve is at a still greater level above that for para ii (due to the higher mortality rate associated with this greater parity group), but there is clearly no deviation from the parallelism seen in Fig. 5. Obviously, a woman who has had five children at the age of 24, has experienced, on the average, shorter intervals between births than one who has had only

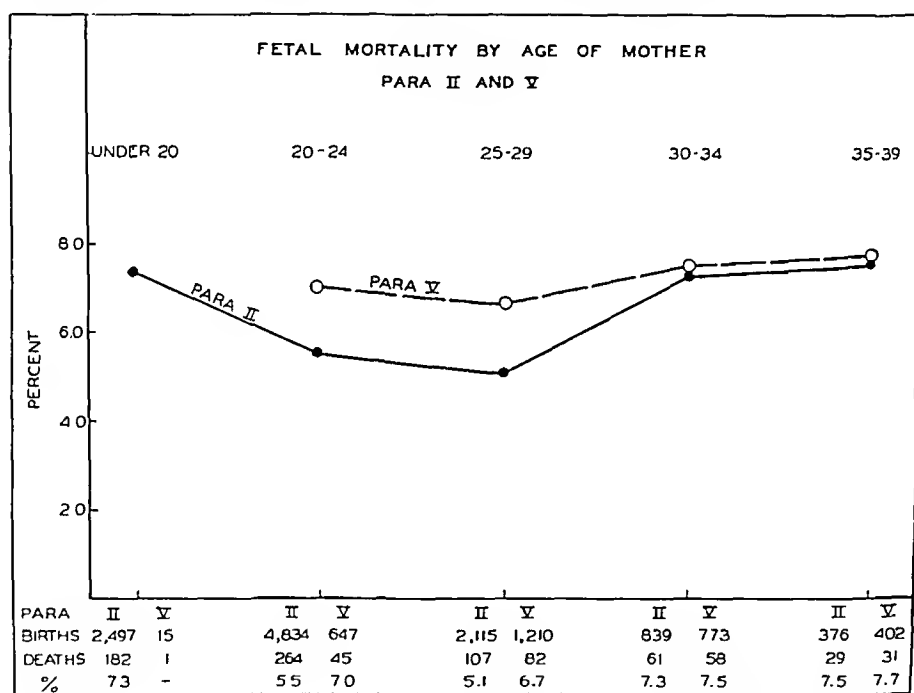


Fig. 6.—The curves of fetal mortality (stillbirth and neonatal) according to age of mother, para ii and para v, only.

two children at that age. But except for an increased mortality due to greater parity, an increase that is proportionate to that observed in other age groups, we find no difference in infant mortality between the para v of 24 and the para ii of the same age. It will be noted, furthermore, that the woman who is having her fifth baby between 20 and 24 faces substantially the same infant mortality as one who is giving birth to her fifth baby between 25 and 29.

In sum, our indirect study has failed to indicate that rapid multiparity, with an average short interval between births, exerts any appreciable effect on infant mortality.

In Fig. 7 similar graphs of infant mortality plotted according to age are shown based on data compiled in New York State (exclusive of New

York City) by Dr. Jacob Yerushalmy, Medical Statistician, U. S. Public Health Service. His findings in regard to para ii and para iv are strikingly similar to ours. His para v group, however, does show a marked upward swing in the 20 to 24 age group, suggesting a harmful effect exerted by rapid multiparity. Both Dr. Yerushalmy's figures and ours in this particular parity and age group are based on less than 1,000 cases and the discrepancy may be due to a sampling error in one or the other series.

Finally, in the indirect study, the maternal mortality of para ii as compared with that of para iv, v and vi (grouped) was in any age group essentially the same. (Table XXIV).

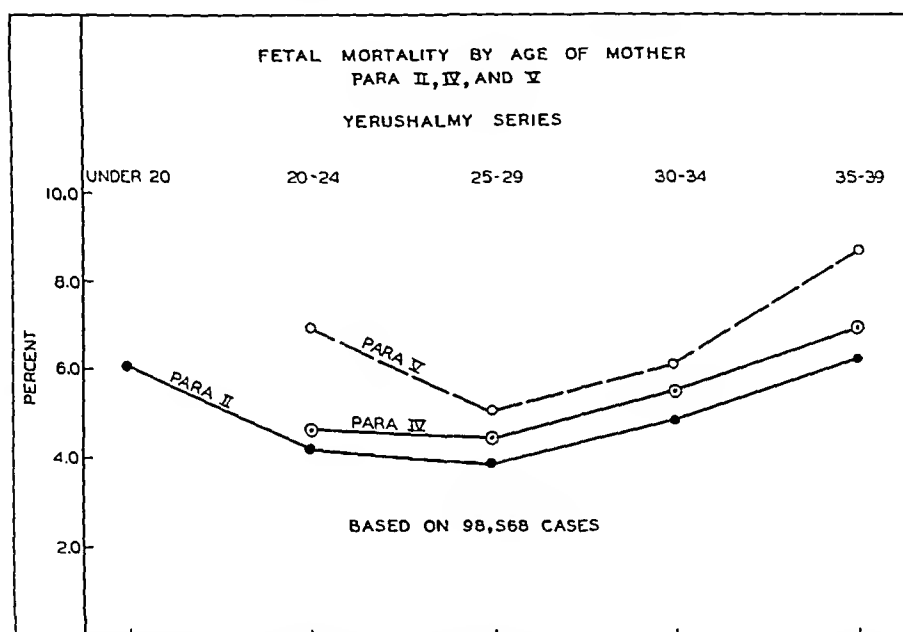


Fig. 7.—Fetal mortality according to age of mother, para ii, iv and v, based on data compiled by Dr. Jacob Yerushalmy.

TABLE XXIV. MATERNAL MORTALITY OF PARA II COMPARED WITH THAT OF PARA IV, V AND VI (GROUPED), ACCORDING TO AGE

	UNDER 20	20 TO 24	25 TO 29	30 TO 34	35+
Para II					
Cases	2,479	4,797	2,092	839	372
Deaths	6	13	4	8	3
Per cent	0.24	0.27	0.19	0.95	0.81
Para IV, V and VI					
Cases	107	2,358	3,493	2,200	1,210
Deaths	0	6	8	17	12
Per cent	0.00	0.25	0.23	0.77	0.99

### Summary and Conclusions

When the data reviewed in this study are analyzed from the viewpoint of their statistical validity, it becomes clear that certain of the findings are significant beyond question, while others are only on the borderline



of statistical significance and hence must be regarded as suggestive only. In the former category the following conclusions seem clear-cut and inescapable: (1) Infants born from twelve to twenty-four months after a previous viable delivery (that is, during the second year) have at least as low a stillbirth and neonatal mortality as do infants born after longer intervals. (2) The longer the interval between births, the more likely the mother is to suffer from some form of hypertensive toxemia of pregnancy. The incidence of this complication is lowest when the interval is twelve to twenty-four months, significantly higher when it is twenty-four to forty-eight months, and much higher when it exceeds four years. In the present study this was equally true of white and colored ward and private patients. (3) In patients who have had a previous hypertensive toxemia of pregnancy, the likelihood of repetition becomes progressively greater as the interval becomes longer. (4) The incidence of the following conditions is no greater when the interval is twelve to twenty-four months than when it is longer: premature labor, anemia, post-partum hemorrhage, and puerperal infection; nor are mothers in this brief interval group less able to nurse their babies. The weight of the mature babies was approximately the same regardless of the interval.

Among those findings in the study which are on the borderline of statistical significance, the trend in the neonatal mortality is perhaps the most suggestive. This was 1.5 per cent for the 'Brief' interval group, 2.2 per cent for the 'Moderate' group, and 2.6 per cent for the 'Long' group. The difference between the first two of these percentages is 1.5 times the standard error of the difference; in other words, the odds are about 6 to 1 against the likelihood that this difference is due to a sampling error. The difference between the first and third of these percentages is 2.0 times the standard error of the difference; in other words, the odds are about 20 to 1 against the chance that this difference is due to a sampling error. When it is further recalled that hypertensive toxemia of pregnancy increases progressively in each of these three groups and that this complication is a frequent cause of premature delivery and hence neonatal death, the upward trend in our neonatal mortality as the interval increases becomes all the more plausible. But let it be emphasized again that our figures do not prove it, but merely suggest the probability.

Most tenuous of all inferences to be drawn from this study are those which have to do with the 'Very Brief' interval group. Not only is the number of cases in this group very small, but other difficulties in analysis present themselves, particularly the time element. While we feel sure that this time element accounts in large measure for the high incidence of abortion and premature labor in this group, we cannot be sure that it is wholly responsible; and, as indicated, there is suggestive evidence that pregnancies which are conceived within five months after a previous delivery show a slightly higher incidence of premature termination.

Finally, concerning the bearing of our findings on the practical issue of child spacing, the following question would seem permissible. In recommending child spacing for the health of mother and infant, have we not overlooked the greatest talisman that a pregnant woman can possess, namely, Youth? Child spacing, by definition, means maternal aging; and after a certain optimum period, probably in the early twenties, maternal aging means inevitably somewhat higher risks both to mother and child. All experience and all statistics support this statement. It would seem almost inconceivable that a mere difference in age of four years or so could have any appreciable effect on the outcome of childbearing, yet in any considerable series such as this, it manifests its influence unmistakably; and whatever advantage is gained by a rest period of several years between births seems to be offset, and in some respects more than counterbalanced by the aging factor. For the best maternal and fetal outlook we are inclined to believe that Youth is a better ally than child spacing.

The author is greatly indebted to Dr. Jacob Yerushalmy, Medical Statistician, U. S. Public Health Service, for advice and active help in the preparation of the statistical data presented in this paper. However, the interpretation of the data and the conclusions drawn are solely the responsibility of the author.

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### Discussion

DR. WILLIAM J. DIECKMANN.—Dr. Eastman has made a very thorough study of an important subject about which little is known. He could have drawn various sensational conclusions, but he has simply pointed out that his critical group, namely, those with an interval of one year, was too small for wide comparisons.

Adair mentions that the minimum time between labors should be 18 months. Sellheim states that pregnancy, lactation, and involution and regressive changes each require nine months. He suggests, therefore, that the proper spacing is three years between labors. He stated that the second and third babies had a lower mortality than the first but the fetal mortality steadily increases after the third. The Metropolitan Life Insurance Company reports that there is a slightly lowered mortality for married women between 25 and 45 than for single. Isenhour and co-workers studied blood pressure levels in parous and nulliparous women from 20 to 60 plus years. No difference could be noted in the incidence of hypertension and average blood pressure levels of these two groups of women. They stated that hypertension following a toxemia of pregnancy is not the result of this complication of pregnancy, but rather that toxemia occurs most frequently in patients with predisposition for vascular disease.

I have always taught that the interval between pregnancies should be two years, but for the past eight years, where the patient had sufficient income to provide proper

food, private care, and some help at home, I have told the patient that she may have another baby within 12 to 18 months. I was influenced in my change by several women who deliberately had their babies, two or three, as close as possible. Their reasons were that they wished the "diaper stage" at one time, that their activities already restricted by one baby would not be further affected by more, and finally, that the children with a short interval between were better companions for each other.

In clinic patients, I have been studying the blood, as well as the renal function, heart size, etc., in patients who have had ten or more children. I do not believe that pregnancy causes injury to the normal woman. I have one patient who in 1942, when 46 years old, had her seventeenth baby. There were no abortions and only one baby died. These 17 pregnancies occurred in a period of 26 years. We delivered the last seven babies, the final two pregnancies being complicated by hypertension. Obviously this patient now has an essential hypertension resulting from her age and a predisposition for vascular disease.

Woodbury's study is based on a very low income group and is, therefore, not applicable to general maternal and fetal complications and mortality.

Eastman reports that the premature mortality in his group with less than a year between pregnancies was relatively high, but that the number is too small for definite conclusions. He could find no difference for anemia, although I would expect such to exist. Post-partum hemorrhage and puerperal infection showed no change as one would expect. He emphasizes that the incidence of toxemia increases with each longer interval.

We have just completed a study of 490 toxemic patients who had two or more viable babies in our hospital. With intervals of two years, three to four, five to six, and seven to eight years, the incidence of recurrence of toxemia was 37 per cent in the first group, 47 in the second, 60 in the third, and 64 per cent in the last. Our data also show that with increasing age, the incidence of recurrence of toxemia increases. Obviously, patients who had a toxemia of pregnancy should not wait two or more years before the next pregnancy.

I have been stating for a number of years that many patients have a predisposition to vascular disease which first manifests itself in pregnancy. Furthermore, I have pointed out that if a patient has a toxemia in one pregnancy and then is found ten years later to have a hypertension, the probabilities are that the vascular disease is simply the result again of age plus a predisposition. It is pleasing to have confirmation of this from Eastman's study as well as from Stander's clinic.

Eastman's final sentence, which I most heartily endorse, is "For the best maternal and fetal outlook we are inclined to believe it is better to rely on Youth than on Child Spacing."

DR. WILLIAM C. DANFORTH.—It is remarkable how an error once published, is quoted and repeated indefinitely. The study to which we have just listened has clearly shown how failure to evaluate all the facts may lead to wrong conclusions. In carefully analyzing his figures, and in drawing the proper conclusions from them, Doctor Eastman has done us a service and it is to be hoped that his results may attain their deserved publicity.

The work which has been presented here tonight is timely. We are engaged in a great war in which the wastage of life cannot fail to be great. The need for the replacement of those who do not return will soon be felt. It is important, too, that the replacement should come from that part of the people which is capable, physically and mentally, of producing a new generation which will be able to cope with the problems of the future.

As I cannot question either the accuracy of Doctor Eastman's figures or the validity of the conclusions he draws, I beg leave to take a moment to point out a

further implication of this work. As Doctor Eastman has said, the advocates of birth control were quick to seize upon the conclusions of Woodbury.

Birth control, child spacing or planned parenthood, all of which mean the same thing, are concerned with the problem presented by the individual family. As physicians, as men whose lifework is the management of the reproductive process and the ills peculiar to women, and as citizens who have enjoyed more than the average opportunity for the acquisition of knowledge concerning social and community problems, it seems to me that we should look further than this. While conceding that the individual woman may be benefited, what is the result upon the nation as a whole? It has been my experience that the most eager searchers after information concerning contraception are those of the upper intellectual and economic levels. Families among these, the more responsible of our citizens, are limited while far less limitation is found among the irresponsibles and the less efficient. What will be the long range effect upon the country of limited reproduction among those who may logically be expected to produce the best quality of offspring?

Statisticians tell us that a minimum of three children per family is needed to maintain the population at a given level. This is true today with our greatly improved methods of infant care. One hundred years ago, six were needed. If we regard the number of births needed to maintain population at its present level as represented by 100, it is shown by Dublin that, during the time represented by the years 1935 to 1940, the net urban reproduction rate was only 74 per cent. During this same period the rural rate was 144 per cent. The average rate was 96 per cent. Part of this rural excess was in backward parts of the country, in which education and even nutrition were defective. In these areas stock of less than full value was produced. The 96 per cent, therefore, is scarcely worth its face value. We have not as yet attained the low rates found in other countries, as for example, 74 per cent in England and Wales in 1933, but any rate of reproduction which is less than enough to maintain the population level cannot be looked upon as a sign of national health. Had not the decline in the birth rate in the last century been accompanied by a marked decline in the death rate, the result would have been serious.

The statistical studies of Dublin also show that much of the upswing of births in the past two years has taken place in first and to a lesser degree, in second, births. This is only slightly evident in third births and from that point on, the decline continues. The present increase in the birth rate must be regarded as temporary and occasioned by the wave of marriages caused by the outbreak of war.

It is important to society as a whole that the lives and the health of women be protected. They are the producers of children, they bring up the children and have the greatest part in their early training and they are the centers of the homes. There is no class of citizens more valuable to the country than women of childbearing age. Anything which renders the giving of this service safer and pleasanter is worthwhile, not only to them but to all of us. But, in order that the desires of each individual family shall be consulted as to the number, usually a small one, of the children which they shall have, let us not lose sight of the extremely important question of the production of the next generation of our national family. It will require but a few generations insufficient in numbers to cause a marked decrease in the population as a whole. But a few generations in which the reproduction has been largely in the ranks of those of lesser intelligence and physical vigor will stunt the mental and physical strength of the nation, perhaps to a dangerous extent. The need for waging two great wars within the space of one generation should warn us that this is a dangerous prospect. It has been said that birth control gives us the power to determine not only the size but the character of the nation. Such figures as have been published concerning the reproduction rates of college men and women, for example, give but little cause to exult over the influence it exercises over the character.

The evidence presented here tonight shows that, apart from the very brief group, in which premature deliveries vitiate the fetal mortality figures, neither the fetal nor the maternal mortality is materially affected. This should remove some of the fears which some, at least, in this country have had, that the having of a fair sized family is a menace. It is indeed youth upon which we must rely rather than upon child spacing.

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Adam, G. Shedden: *The Rh Factor and Its Application to Obstetric Practice*, M. J. Australia 1: 507, 1943.

The author reviews the history of the Rh factor in relationship to blood transfusion, and stresses its importance in obstetric practice. In obstetrics the chief point of consideration is the concept of iso-immunization in the human body by the Rh factor. This has thrown new light on the etiology of erythroblastosis fetalis. In regard to blood transfusion, if the woman requires a blood transfusion during her pregnancy or puerperium, it is best not to use the husband for the donor even though he is of the same blood group. It is advised that stocks of serum containing the anti-Rh factor be built up. In transfusing a baby with icterus gravis neonatorum, the mother's blood should not be used since the body is almost certainly "Rh positive" and the mother's blood contains the Rh antibody which will only destroy more of the infant's red cells. The father is also not a suitable donor for his red cells would be destroyed by the presence of the Rh antibody (acquired from the mother) in the infant's serum. The most suitable donor is obviously one whose blood is "Rh negative" and does not contain the Rh antibody.

WILLIAM BERMAN.

Young, James: *Maternal and Child Health: The University and the Public Health Services*, Edinburgh M. J. 50: 474, 1943.

Dr. Young outlines in this article the planning of the future services which concern the health of the mother and child. He states these plans require the necessity of making arrangements for the training of doctors, consultants, nurses, health visitors and social workers who will be responsible for maternal and child welfare.

These arrangements include, (1) the establishment of adequate departments of maternal and child health in the medical schools and universities, (2) intimate collaboration between these departments of maternal and child health and the maternity and child welfare and school medical services of the health authorities.

The author stresses the fact, too often overlooked and neglected in this country, that *organizations of services designed to give adequate care to mother and child must be so developed as to provide a continuity of supervision from the prenatal period to school age.*

CLAIR E. FOLSOME.

## THE BIOLOGIC CHARACTERISTICS OF THE NORMAL VAGINA\*†

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### Introduction

IT IS now generally conceded that the biologic characteristics of the normal human vagina during the sexually mature period of life are governed by the ovarian hormones. It has been established beyond doubt that the estrogens are the primary factors responsible for the proliferation of the vaginal epithelium, and there is also very good evidence that, in the human and in the monkey, it is the estrogens which mediate the deposition of glycogen in the vaginal epithelial cells. Progesterone appears to play some part in the further differentiation of these cells and possibly also influences some of the biochemical characteristics of the vaginal tract, but the evidence on this score is still meager. Beyond this, much controversy continues to exist on the mechanism by which the vaginal glycogen is metabolized and on the origin and nature of the enzymes involved in the fermentation of the carbohydrates to acid. The same uncertainty also exists as to whether the lactic acid, which is responsible for at least most of the vaginal acidity, is produced as an end product in this enzymatic process or whether the conversion of carbohydrates to lactic acid results from the action of certain bacteria particularly the lactobacilli of Döderlein. Nor is it yet settled that these biochemical reactions determine the type of flora which can inhabit the vagina or whether the converse is true, namely, that the presence of certain organisms in the vaginal tract will strongly influence certain of the biochemical reactions of the vagina.

To these problems have recently been added the difficulties of defining subtle but yet important alterations in the vagina occurring rhythmically in association with the ovarian cycle. Such periodic differences in the histology and cytology of the vagina are now quite generally accepted, and data are accumulating on similar cyclic variations in some of the normal biochemical characteristics such as glycogen content and vaginal acidity.

\*Read at a meeting of the Philadelphia Obstetrical Society, October 7, 1943.

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These problems assume more than theoretical significance when one attempts to define the normal vagina and to establish various abnormal or pathologic states upon this basis. It is apparent that, in order to do this, certain criteria based upon well-founded observations must be available by which it will be possible to evaluate at least those factors which may be of clinical significance. Scattered observations on various of these factors in normal patients have been made by many observers, but, unfortunately, little attempt has been made to correlate the various factors in the same patients. In the process of making such routine studies on large numbers of patients, we have accumulated a considerable amount of data on the various biologic factors of the normal vagina. These form the basis of the observations which are here presented in conjunction with a rather detailed discussion of pertinent data in the literature as a critical analysis of what constitute the biologic characteristics of the normal vagina.

### Selection of Patients

It was considered important that the patients selected for this study should be in general good health. Patients with malnutrition, vitamin deficiencies, and other metabolic disturbances were not chosen since these factors may have an important bearing on the health of the vagina not only by their effect on mucous membrane in general, but also because they may influence ovarian function. Patients with any endocrine disturbances, particularly those involving the pituitary-ovarian cycle and also those with thyroid disease, were avoided for similar reasons.

It was also required that the menstrual cycle should be reasonably normal. Those patients were chosen in whom the menses recurred regularly at intervals of 26 to 30 days with a flow of from 3 to 7 days and who had an approximately normal amount of bleeding. A pelvic examination was also made to rule out any gross abnormalities of the uterus and adnexa. Moderate malpositions of the uterus were overlooked as having little significance. The patients were carefully questioned to rule out the presence of symptoms suggesting any vaginal abnormalities such as excessive discharge, local irritation, burning, itching, heat, dyspareunia, and dysuria. It was required also that the patients should not employ any local treatment or medicaments such as douches, jellies, suppositories, and the like. Patients were asked to refrain from coitus for 24 hours preceding examination. These patients had no knowledge of contraceptive measures or did not employ them except for the practice of withdrawal.

A thorough examination of the lower genital tract was made at each visit as follows: The vagina was exposed with a bivalve speculum, without the use of a lubricant, and the vagina and cervix were then carefully inspected for the presence of any abnormalities, particularly with respect to evidences of irritation, inflammation, ulceration, or erosion.

The vaginal and cervical discharges were then carefully inspected and a note made concerning the amount, color, consistency, character and odor. The special studies which were then made included determinations of the pH of the vaginal mucosa at several levels; the preparation and examination of vaginal smears for cytologic study, glycogen content, and bacterial flora; examination of fresh wet vaginal smears for parasites and cellular content, and the removal of small vaginal biopsies for routine histologic study and special glycogen stains. The details of the methods employed for these studies will be given separately as each factor is discussed.

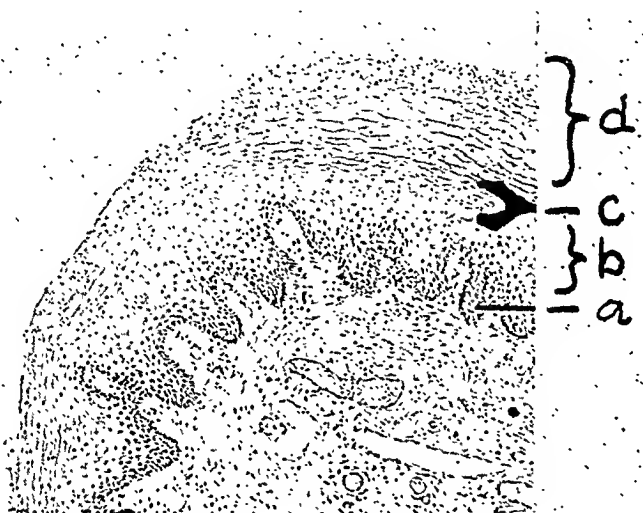


Fig. 1.—Normal vaginal mucosa.

- (a) Dark zone of basalis
- (b) Light zone of basalis
- (c) Dierks' intraepithelial zone of cornification
- (d) Superficial or functional layer

We have accumulated such data on more than 500 patients; however, there were only 37 normal patients among these in whom we were able to obtain satisfactory studies 3 times weekly through one to three menstrual cycles. These latter form the basis for most of the normal values herein presented.

### I. The Endocrine Factor

In order to fully appreciate the influence of the ovarian hormones on the vaginal mucosa, it is necessary to be fully familiar with the histologic characteristics of this structure. This may best be described in terms of the normal as it occurs in the sexually mature female (Fig. 1).

The vaginal epithelium is supported upon a thick, well-developed, connective tissue layer or tunica propria, rich in small blood vessels and lymphatics. Just beneath the fine basement membrane (lamina propria), small numbers of leucocytes are present which are generally of the lymphocytic and monocytic series. A moderate variation in the number



of leucocytes in the subepithelial layer occurs throughout the cycle, but aggregations of large numbers of these cells are abnormal, often being one of the earliest findings of an inflammatory lesion of the vagina. The vaginal epithelium itself consists of a number of layers some of which are inconstant and have been variously indicated by different observers. The deepest layer is generally referred to as the basalis and is made up of one or more rows of deeply staining cells (the "dark zone") and a larger number of rows of less compact cells with weaker affinity for the basic stain (the "light zone"). The dark zone may consist of a ribbon of deeply staining cuboidal cells with large dark nuclei, or, in some phases of the cycle during which rapid growth is occurring, it may consist of several rows of such cells. In the light zone of the basalis, the shape of the cells changes as they progress upwards from oval to polygonal to a flat spindle contour. Sharply dividing the basalis from the most superficial layer is a thin dense layer which is not constantly present and which is commonly referred to as Dierk's "intra-epithelial zone of cornification."<sup>1</sup> The cells here are markedly compressed, and the nuclei are also flattened and stained deeply. Within the cells and also in the intracellular spaces are numerous granules of various sizes which impart a characteristic appearance to this layer. The superficial layer above this, commonly referred to as the "functionalis," consists of a varying number of rows of stratified cells which have undergone cornification to a greater or lesser extent. When stained by appropriate methods, the cells of all layers, except the dark zone of the basalis, are found to be rich in glycogen.

### Estrogen Effect

Although some of the earlier German workers hinted at a relationship between ovarian activity and the biologic characteristic of the vagina, the first definite description of such a correlation is generally attributed to Muir<sup>2</sup> who arrived at his conclusions from purely clinical studies. These observations were soon corroborated and further expanded by many workers particularly by Cruikshank and Sharman.<sup>3</sup> The latter demonstrated that, in those periods of life associated with high estrogen levels, namely, in newborn infants up to the third or fourth week of life and in women during the reproductive period, there is a deep many-layered vaginal epithelium rich in glycogen; whereas, in the periods of diminished ovarian function, namely, in childhood and following the menopause, the vaginal epithelium is thin, and glycogen is absent. Cruikshank and Sharman further correlated those periods of high estrogen concentration with a strongly acid secretion and a homogeneous bacterial flora and pointed out that this was particularly true during the latter months of pregnancy where there is an overabundance of estrogen.

The role of the estrogens in inducing proliferation of the vaginal epithelium was described in castrate monkeys by Allen<sup>4</sup> and in female children by Lewis<sup>5</sup> and, subsequently, has been confirmed by numerous

other workers. As the result of the injection of estrogens an enormous growth in the vaginal epithelium can be induced. In spayed monkeys and in postmenopausal women, the few cell layers present may be made to increase to as many as 60 or 80 rows. As pointed out by Allen, one of the first things that is noted as the vaginal epithelium thickens is the increased number of growing bulbs along the basement membrane, the cells of which contain many mitotic figures. The nuclei of the intermediate layers become pyknotic. Sometimes, remnants of nuclei may also be found in the superficial layer, but, more often, these cells are completely cornified although not to so marked a degree as in the rodents. Comparable observations may be made in human vaginal biopsies (Fig. 2).

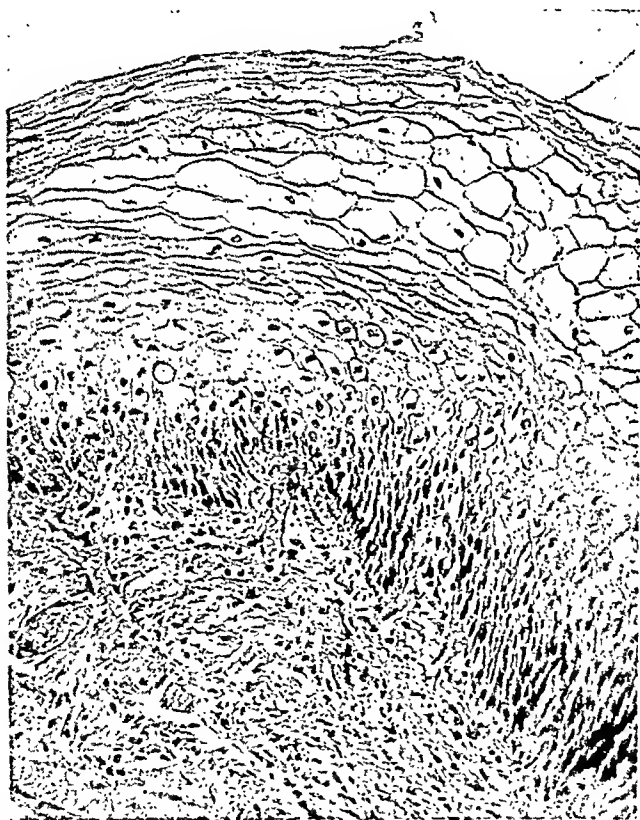


Fig. 2.—Vaginal mucosa at midcycle showing marked activity in the basal layer, pyknotic nuclei in the intermediate layer, and remnants of nuclei in the superficial cornified zone.

In a similar manner, the effect of estrogenic hormone in causing a deposition of glycogen in the vaginal epithelium of monkeys was demonstrated by Robertson, Maddux, and Allen.<sup>6</sup> Like observations were made by Krumm<sup>7</sup> in postclimacteric women and it has since been shown to also occur in children and oophorectomized women by other observers.

*Progesterone.*—The effects of progesterone on vaginal biology are difficult to evaluate. In physiologic dosages, progesterone itself appears to have little effect on the proliferation of the vaginal epithelium.<sup>8</sup> In

large dosages, progesterone will induce some degree of cornification in castrated rodents.<sup>9</sup>

Rakoff<sup>10</sup> has recently shown that, in large dosages (20 to 60 mg.), some degree of vaginal epithelial proliferation and cornification can be induced in castrate and postmenopausal women, although not nearly so marked as is obtained with estrogens.

When estrogen and progesterone are given simultaneously to the castrated rodent, progesterone appears to partially inhibit the estrogen effect.<sup>11</sup> If estrogen is given for a sufficient time to produce full cornification, and then progesterone is added, a similar inhibitory effect may be demonstrated while, if estrogen is added after progesterone, marked cornification is difficult to obtain. From a study of human vaginal smears, it would appear that the regressive changes which are noted during the luteal phase of the cycle are also probably due to the combined action of progesterone and estrogens.

*Androgens.*—In physiologic dosages, the androgens generally cause atrophic changes in the vaginal epithelium of human beings.<sup>12</sup> McCahey and Rakoff<sup>13</sup> showed that, in rats injected with relatively very large dosages of testosterone propionate, some degree of vaginal hyperplasia with some stratification and cornification could be induced. More recently, Clarke and Selye<sup>9</sup> have shown that various hormonally active steroids, whether folliculoids, luteoids, corticoids, or testoids, resulted in some vaginal epithelial growth in the rat when given in sufficient dosages. In the human being, Rakoff<sup>10</sup> found that, after submucosal injection of 25 mg. of testosterone propionate in the vagina of a castrate, some local vaginal hyperplasia resulted although, when given parenterally in dosages up to 300 mg. over a period of 4 to 6 weeks, similar results could not be obtained; indeed, in normal patients, such treatment resulted in atrophic changes.

*Cyclic Changes.*—The presence of cyclic changes in the human vaginal epithelium has been noted on histologic study by Stieve,<sup>14</sup> Dierks,<sup>1</sup> Puecioni,<sup>15</sup> Traut et al.,<sup>16</sup> and others. Although most workers agree that in the human vaginal mucosa during the sexually mature period of life there is a definite rhythm which it is possible to correlate with the ovarian cycle, it is quite obvious that these changes are not very marked and frequently are quite difficult to demonstrate. The reason for this appears to lie in the fact that the cyclic changes in the human vaginal mucosa are quite shallow and fail to go through the marked regression noted in the rodents. Apparently, throughout the menstrual cycle in the human being, there is always sufficient hormone to maintain the basic integrity of the epithelial layers.

In a series of 37 normal patients whom we have followed by weekly biopsies through several menstrual periods, there was very distinct evi-

dence of cyclic alterations. In many respects these were similar to the findings noted in the excellent studies of Davis and Hartman<sup>17</sup> in the rhesus monkey; however, as also noted by Traut and his associates,<sup>16</sup> in many instances these changes were not nearly so clear-cut in the human being, particularly those relating to the superficial and intermediate layers.

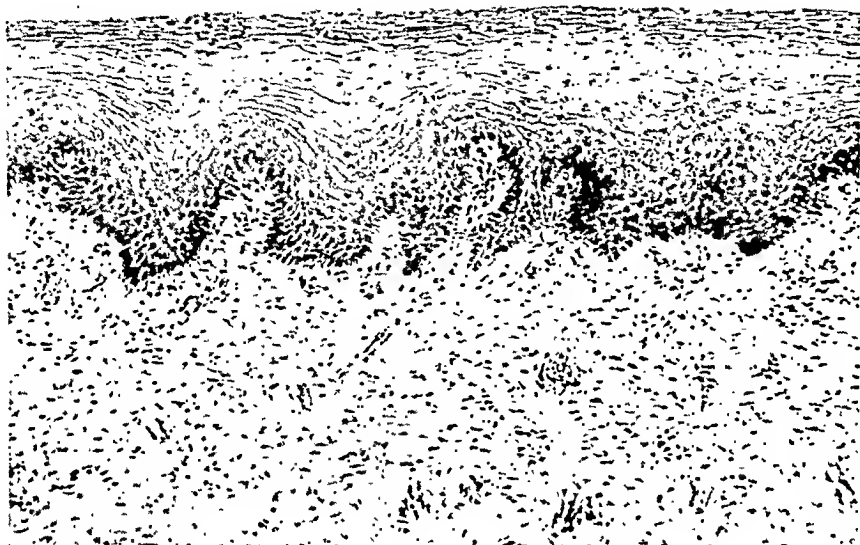


Fig. 3.—Vaginal mucosa, eighth day of the cycle, showing marked proliferation in the dark zone of the basal layer.



Fig. 4.—Vaginal mucosa, twenty-fifth day of the cycle (Best's carmine stain). Note the marked intraepithelial zone of cornification and the desquamation of the superficial layer.

Perhaps the most constant cyclic change noted in our biopsies was the proliferative changes evident in the dark zone of the basalis which in most of our cases was most marked between the seventh and fourteenth days and resulted in an increase in the thickness of the entire basal layer (Fig. 3). In the mideyele, the epithelium frequently attains its greatest thickness since growth and differentiation of the three layers have attained their maximum degree, and desquamation has not yet freely started. In the latter half of the eyele, the changes involve chiefly further cornification and desquamation of the superficial layer. In some instances a considerable thickness of highly cornified cells may remain until quite late in the eyele while, in other cases, whole plaques of cells may separate to the extent that only the basalis remains (Fig. 4). It is quite obvious that these regressive changes are difficult to follow by histologic methods while smear methods are admirably suited to this purpose. One feature of the premenstrual phase which is very often strikingly present in the biopsies is the increase of leucocytes in the sub-epithelial zone which may persist through the menstrual flow; not uncommonly, they may invade the epithelium proper as "wandering" cells and are best seen in the basalis.

In many respects it is far easier to follow these cyclic changes by cytologic studies of the superficial vaginal epithelium. Criteria for studying human smears were worked out by Dierks,<sup>18</sup> Smith,<sup>19</sup> and Papanicolaou.<sup>20</sup> More recently, simpler staining methods have been introduced by Shorr<sup>21</sup> and Papanicolaou,<sup>22</sup> and these have proved to be of considerable clinical usefulness. In the main, our findings in these patients do not materially differ from the excellent studies of Rubenstein<sup>23</sup> and will not be discussed in detail here. Suffice it to say that, as a rule, cyclic alterations could be more distinctly followed by the vaginal smear method than in biopsies and that as a means for orientation with regard to the ovarian cycle vaginal smears are unquestionably preferable. In the presence of inflammation or where interfering external factors have been present such as douches, vaginal smears are likely to be of little benefit whereas some useful information may be had from the biopsy.

## II. Glycogen

*Factors Influencing Deposition of Glycogen.*—During the sexually mature period of life the vaginal mucosa is very rich in glycogen, indeed, next to the liver it probably contains more glycogen than any other tissue of the body. As the vaginal epithelium grows under estrogen stimulation glycogen is deposited in the cells and can easily be demonstrated by special staining methods. This also occurs in the monkey<sup>6</sup> but not in lower animals such as the cow, sheep, pig, or rodents.<sup>3</sup> It has also been demonstrated that the glycogen content is scant or absent in those periods of life associated with low ovarian activity and is high during the reproductive period. It is present in greatest amount late

in pregnancy when the estrogen level is very high. Experimentally it has been shown to increase as cornification progresses.

Very few observations have been made concerning the effects of progesterone on the deposition of glycogen. Guest<sup>24</sup> states that in the castrated monkey, progesterone will not produce this response. Rakoff<sup>10</sup> has noted the deposition of some glycogen in castrate women after 20 mg. of progesterone, but smaller dosages were not effective.



Fig. 5.—Vaginal mucosa (Best's carmine stain). High power magnification of the intermediate and superficial layers to show the granular character of the glycogen in the cells and the diffuse staining of the superficial zone of cornification.

In the human vaginal epithelium glycogen is absent or very scant in the basal layer of cells. The intermediate layer of cells, however, is very rich in glycogen, particularly those nearest the superficial layer. In these cells, glycogen is present in large granules which are easily seen when biopsies are stained by the iodine method, Best's carmine stain or the Feulgen method. In the superficial cornified layer glycogen is also abundantly present but because of the flattened state of the cells the staining is diffuse (Fig. 5). The glycogen in the superficial cells can be better demonstrated in smears than in biopsies. Glycogen per se appears to be present in the cells alone since ordinarily none can be demonstrated in the cell-free vaginal secretion.

The manner in which glycogen comes to be deposited in the vaginal epithelium is not known. In a vaginal biology symposium<sup>24</sup> the prevalent opinion appeared to be that there is a diffusion of glucose from capillaries and lymphatics into the basal layers, the cells of which take up the glucose and change it to glycogen. As the cells in the basal layer migrate toward the surface, glycogen becomes more abundant in the intermediate and superficial layers. It is postulated that this property of the conversion of glucose to glycogen is a specialized function of the vaginal epithelium since it does not occur in other similar epithelial structures such as the mucosa of the esophagus.

From chemical studies of the vaginas of monkeys Van Dyke and Ch'en<sup>25</sup> found that the concentration of glycogen was highest in the upper part of the vagina ranging from 2.36 to 2.98 per cent; in the midvagina it ranged from 1.93 to 2.48 per cent while in the lowest part of the vagina it was 0.64 per cent. They also demonstrated that after ovariectomy the concentration in the midvagina fell to less than 1 per cent but after injection of estrogens increased to as high as 4.42 per cent. Similar conclusions were reached by Krumm<sup>7</sup> by the rather approximate method of directly applying iodine to the vaginal wall (Schiller test) and noting that the portio vaginalis and fornices take the deepest stain while the mucosa of the lower half of the vagina takes very little stain.

Rakoff<sup>10</sup> made glycogen determinations on strips of vaginal mucosa obtained from two normal young women at operation. The strips were taken from the anterior or posterior fornix, middle third of the vagina and lower third of the vagina. The epithelium was stripped away from the mucosa so that on section it consisted almost entirely of epithelium and lamina. The tissue was dropped at once into absolute alcohol and glycogen determined after conversion to glucose. In the vaginal fornices glycogen ranged from 2.5 to 3.0 mg. per cent, in the middle third from 1.5 to 1.8 mg. per cent and in the lower third of the vagina from 0.6 to 0.9 mg. per cent.

Some valuable studies on the lability of the vaginal glycogen have also been made by Van Dyke and Ch'en. They showed that following starvation the glycogen of the vaginal mucosa in the monkey is not appreciably reduced although, as is well known, the concentration of hepatic glycogen was markedly lowered. Similarly, the concentration of vaginal mucosa glycogen was not affected by large doses of thyroxin, whereas there was a marked reduction in hepatic glycogen. They concluded therefore, that the only method for reducing the concentration of glycogen in the vaginal mucosa so far discovered is that of bilateral ovariectomy. From more recent studies it seems that the same effect may be accomplished by the administration of androgens.<sup>26</sup> The underlying mechanism of course may be similar, namely, an interference of the estrogen effect on the vaginal mucosa.

*Factors Influencing the Utilization of Glycogen.*—It has long been assumed that the glycogen of the vaginal mucosa is converted into simpler carbohydrates and then into lactic acid and is thus the primary source of the vaginal acidity in the human being. Much difference of opinion exists, however, as to just how this is accomplished. The possibilities which have been suggested are the following:

(1) *Glycogen is attacked directly by certain bacteria (particularly the lactobacillus of Döderlein) and converted into lactic acid.* This was the hypothesis favored by Zweifel<sup>27</sup> and later supported by Schultheiss<sup>28</sup> who claimed that under suitable conditions Döderlein's bacillus can directly attack and break down glycogen with the production of lactic acid: this could not be supported by the work of Smordinzew and Kott<sup>29</sup> but was confirmed by the in vitro experiments of Cruickshank<sup>30</sup> in which he demonstrated that Döderlein's bacillus and it alone, of the organisms likely to be present in the vagina as saprophytes or pathogens, is capable of directly fermenting glycogen with the production of acid.

(2) *Glycogen is partly fermented to simpler carbohydrates by enzymes present in the vagina; these are then further reduced by Döderlein's bacillus.* A number of workers have assumed that glycogen must first be converted to simpler sugars before it can be utilized by Döderlein's bacillus. This theory would explain the observation<sup>3</sup> that although the vaginal secretion was moderately acid shortly after birth, the acidity becomes further increased after 3 or 4 days when Döderlein's bacilli appear. Guest<sup>24</sup> has also made some observations indicating that in the vaginal wall there is a certain amount of carbohydrate of a lower molecular weight than glycogen, which does not stain with iodine or Best's carmine. He also believes that the material that does stain may not be free glycogen entirely since glycoproteins may also be stained by these methods.

(3) *Bacteria other than Döderlein's bacilli are capable of further fermenting the carbohydrates resulting from enzymatic breakdown of glycogen.* This viewpoint has been favored particularly by Weinstein and his associates<sup>31-32</sup> on the basis that in observations on monkeys and postclimacteric women treated with estrogens, there appeared to be very little correlation between the degree of acidity of the vaginal mucosa and the number of Döderlein's bacilli which can be demonstrated by cultures. This conclusion is not in accord with the majority of clinical studies. From their data the above workers suggest that the glycogen is broken down to simpler sugars by some enzymatic action and these monosaccharides are attacked by other bacteria such as *E. coli*, *B. acrogenes*, staphylococci, and streptococci. The resulting acid is inimical to these organisms and by killing them allows the Döderlein's bacillus to become the predominant type.<sup>31, 33</sup>

(4) *Glycogen is converted to lactic acid by enzymatic action alone.* This theory has been supported by the observation that in newborn



children the vaginal secretion is distinctly acid, usually, pH 5.0 to 5.8 even before bacterial implantation occurs, and that lactic acid is already present at that time. Blair-Bell<sup>34</sup> also found lactic acid in hematocolpos fluid which was sterile. Although Cruickshank<sup>30</sup> was unable to demonstrate a nonbacterial enzyme in vaginal secretion, he admitted that in

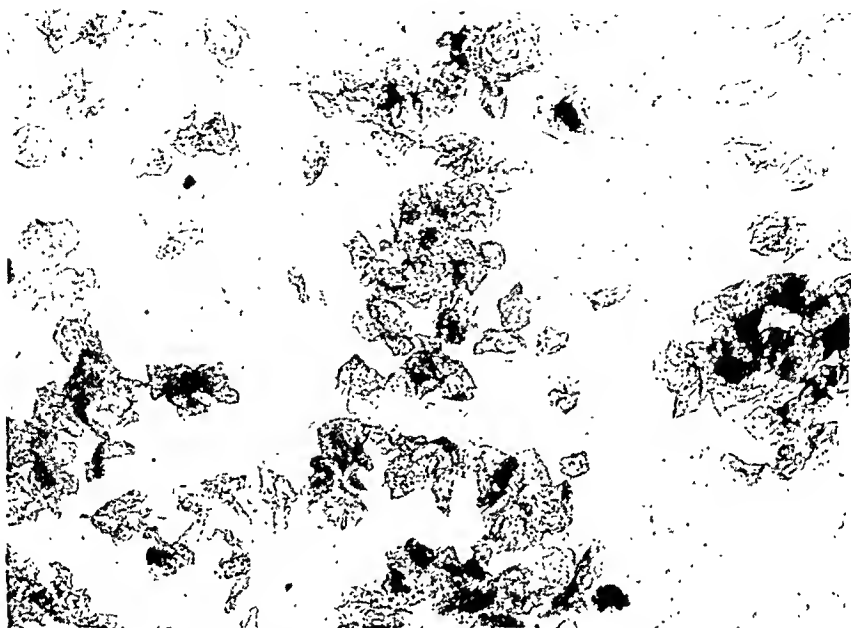


Fig. 6.—Vaginal smear glycogen stain showing moderately heavy concentration of glycogen in most of the epithelial cells (+3).

view of the presence of glycogenase in fresh serum the glycogen in the vaginal cells may be converted in the absence of bacteria by such an enzyme to glucose from which, in turn, lactic acid is produced by a glyeolytic cellular enzyme. A number of other workers<sup>35</sup> have also been unable to demonstrate enzymatic activity in cell-free vaginal fluid, but have intimated that such enzymes may have been destroyed by the technical procedures involved.

*Observations of Glycogen in the Vaginal Epithelium.*—In our studies the glycogen content of the vaginal epithelium was determined from vaginal smears and biopsies prepared with glycogen stains.

The smears were taken from the lateral wall of the exposed vagina with a cotton-tipped applicator. The smear was permitted to dry and then treated as follows: it was fixed in absolute alcohol, and then allowed to dry, after which it was stained with Lugol's iodine solution for 3 minutes and again dried; the excess iodine was then removed by washing with 95 per cent alcohol. When the smear dried it was examined microscopically. Glycogen is indicated by a diffuse red-brown stain of the epithelial cells, the intensity of which depends on the amount of glycogen present. This may be indicated by grading the smears by

comparison with standards from 0 to plus 4 (Fig. 6). If desired, the staining of the glycogen granules may be made more permanent by treating with a dilute solution of  $\text{HgSO}_4$  after staining with Lugol's solution, as suggested by Mancini and Celani-Barry.<sup>36</sup> The glycogen granules retain a deposit of  $\text{HgI}_2$ . Another satisfactory method<sup>37</sup> is to add Lugol's solution directly to a suspension of fresh vaginal secretion and to examine it in the wet state. Mack<sup>38</sup> has suggested exposing the slide to the vapors of Lugol's solution as a staining method. It is, of course, appreciated that these methods indicate only the amount of glycogen in the *superficial* vaginal epithelium and that they are only roughly quantitative. For most clinical purposes, however, these methods appear to be very satisfactory, and have even been suggested as an objective guide to estrogen therapy.<sup>39</sup>

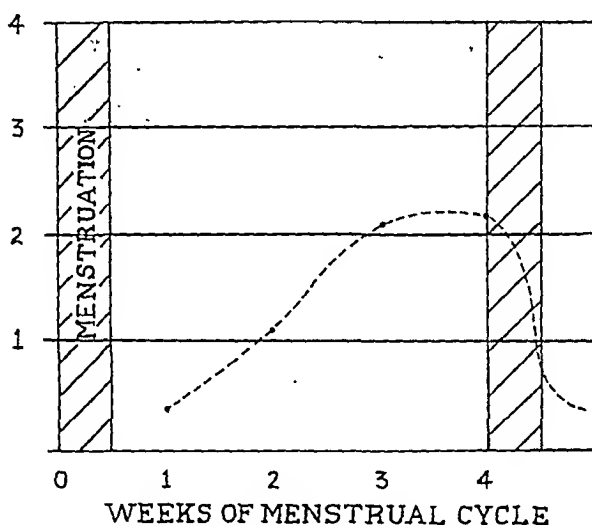


Fig. 7.—Average glycogen readings of 372 iodine-stained smears from 37 women taken at various phases through one to three menstrual cycles.

- 0 = None demonstrable
- 1 = Distinct traces
- 2 = Moderate staining
- 3 = Deep staining
- 4 = Intense staining

From the study of 372 smears from 37 women prepared at frequent intervals throughout the cycle (Fig. 7) it is apparent that an increase in the intensity of the glycogen stain is generally noted at about the time of midcycle. This generally increases further until a peak is reached in the last week of the cycle; a few days before the onset of menstruation a very distinct fall in glycogen concentration is commonly noted. This fall generally occurs at about the time when the disintegrative changes in the vaginal cells characteristic of the late premenstrual phase are noted. It will be noted that the smoothed curve of our observations on the cyclic variations in glycogen content in these 37 cases roughly corresponds to the curve for estrogen excretion.

In our studies the glycogen content of the whole vaginal epithelium was determined from punch biopsies. These were fixed in absolute alcohol or a fixative consisting of 9 parts of absolute ethyl alcohol to 1 part of 40 per cent formaldehyde neutralized with  $\text{MgCO}_3$ . We have tried several of the methods commonly employed<sup>40</sup> including the Best's carmine, iodine and Bauer-Feulgen methods, but for general use we prefer Best's carmine stain.

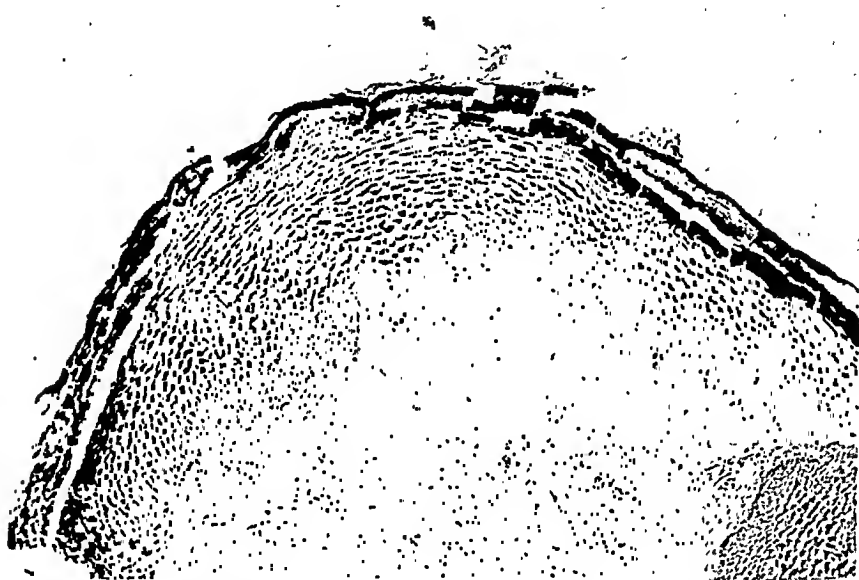


Fig. 8.—Vaginal mucosa (Best's carmine stain) tenth day of the cycle, showing heavy concentration of glycogen in all layers except the dark zone of the basalis.

It is quite obvious that the glycogen-stained biopsies afford information quite different from glycogen-stained smears. The former are an indicator of the glycogen content throughout the thickness of the epithelial layer and afford information concerning the distribution of glycogen in the various layers, and some indication of its physical nature within the cells proper. On the other hand, biopsies are not as easily prepared nor can they be taken so frequently as can smears; furthermore, in the normal vagina the concentration of glycogen in the superficial epithelium as shown by the smear method appears to be a much better indicator of cyclic alterations than can be obtained from the biopsies.

Examination of a typical vaginal biopsy stained by the Best-carminic method (Fig. 8) reveals that glycogen is usually absent from the basal layer of cells, although occasionally, particularly in biopsies taken during the luteal phase, discrete granules of glycogen taking the beautiful metallic carmine stain, may be noted in the rapidly dividing basal cells. The amount of glycogen gradually increases as one approaches the middle zone of the intermediate layer and then becomes quite heavy until the superficial layer is reached. Here the concentration of glycogen is also high, but very often is present in a diffusible form which uniformly

stains the entire cell. The glycogen, however, appears to be contained entirely within the cells proper since none of the stained material is noted in the intracellular spaces. From a study of these specimens one obtains the impression that the glycogen, as such, is formed primarily in the intermediate layer of cells and is converted into a more easily utilizable form in the keratinized cells of the superficial layer.

*Glucose.*—The presence of reducing substances, probably glucose, in the vaginal secretion has long been known, although as already indicated there is much disagreement concerning its origin. The quantity present is reported to vary from zero up to 4 per cent of the fluid. At present it has not been possible to correlate the concentration of glucose with either the pH, the phases of the menstrual cycle, or the amount of lactic acid present.<sup>41</sup> This is not surprising, however, in view of the fact that glucose is probably an intermediary product which is undergoing rapid alteration. It has been suggested that the glucose thus formed may serve as a source of energy for the spermatozoa. On the other hand, MacLeod<sup>42</sup> points out that glycogen can be used directly by the sperm since it possesses an enzyme which can break it down.

### III. Vaginal Acidity

Zweifel, who demonstrated in 1877<sup>43</sup> that the vaginal discharge is usually acid, also determined that the acidity was due to lactic acid and showed later<sup>27</sup> that it was present as racemic lactic acid both in free and bound form. It has since been generally accepted that the acidity of the vaginal secretion is due in most part, if not entirely, to lactic acid, the concentration of which may reach as high as 2 to 3 per cent.<sup>24</sup> The possibility that other acids may also be present was suggested by von Jasche<sup>41</sup> since he did not find any correlation between the glycogen of the vaginal epithelium and the lactic acid content. It is now generally agreed, however, that, provided there is no infection or other abnormality present, high degrees of vaginal acidity are generally associated with an abundance of glycogen, whereas the acidity is markedly reduced when the glycogen is scant or absent due to hypo-estrogenism. It has not yet been possible to demonstrate a strictly quantitative relationship of the glycogen content and the vaginal acidity through the cycle. Indeed, it would be rather surprising if such a relationship exists since the opposing factors of glycogen deposition and glycogen utilization are occurring simultaneously; also very little attention has been given to the possibility that the acidity of the vagina may be, in part, the result of factors other than the fermentation of glycogen. Although it is well recognized that the acidity is greatest in those life phases in which glycogen is present, the fact remains that in childhood and in the postmenopausal period, acid reactions of pH 5.5 to 6.5 are not uncommon. Furthermore, it has been shown by Beilly<sup>44</sup> that in the rat, a species in which glycogen is entirely absent from the vaginal mucosa, the pH undergoes a marked cyclic variation and during estrus falls to

about 4.5 while during the diestrus stage, the readings may approach a pH of 7.0. No explanation of the mechanism of these pH changes is offered except that they are apparently dependent in some way upon estrogenic hormone.

Even in the early studies on vaginal biology there was considerable interest displayed in the degree of vaginal acidity since it had been demonstrated that in various abnormal conditions this became reduced, and it was believed that a normal degree of acidity served as a protective mechanism in preventing the growth of various pathogenic organisms in the genital tract. Since then, many observers have pointed out that there is a distinct correlation between the degree of vaginal acidity and the type of vaginal flora; the acidity being highest in vaginal secretion containing Döderlein's bacilli alone (Grade I) and lowest where Döderlein's bacilli are absent (Grade III).

Further interest in making accurate determinations of the vaginal pH was stimulated by the possibility that distinct changes could be demonstrated in correlation with the ovarian cycle. In fact, from the experience which has thus far accumulated there is good reason to believe that such is the case, although there are often many factors in the patient which tend to obscure this correlation, and certain technical difficulties which may interfere with the accuracy of the determinations. Among these factors are the following: (1) the amount of secretion available in normal cases is often very scant and occasionally no free discharge at all can be recovered; (2) the discharge may be contaminated with cervical secretion; (3) any type of mechanical manipulation such as digital examination or coitus will lower the vaginal acidity; (4) the vaginal pH will also be altered if vaginal douches and other intravaginal medication are employed within 24 hours preceding the determination; (5) if there is any type of inflammatory lesion present the vaginal acidity will also be lowered; (6) even the presence of nonpathogenic bacteria of various kinds will change the vaginal pH. It is therefore apparent that the results obtained will not be a true indicator of the normal biochemical mechanism if any of these interfering factors are present.

*pH in Various Phases of Life.*—From the data now available it is quite apparent that the pH range varies in different life phases in association with estrogenic function. In studies conducted on a group of newborn infants Cruickshank and Sharman<sup>3</sup> obtained the following results:

AGE	RANGE	AVERAGE
First 24 hours	5.3 to 6.4	5.7
Second day	4.6 to 6.4	5.6
Third day	4.7 to 6.8	4.9
Fourth day	4.7 to 5.6	4.8
Ninth day		4.9
	Approximately	
Three to four weeks	5.0 to 7.0	
Six to eight weeks	5.0 to 8.0	

They concluded that from birth until the ninth day the reaction of the secretion was acid, being highly acid from the third to the ninth day, whereas at 3 to 6 weeks it was generally near neutrality. During the remainder of childhood and until puberty is approached, the vaginal secretion remains nearly neutral, generally being slightly alkaline. The pH in children from 2 to 8 years usually falls in the range from pH of 6.0 to 8.0. Near puberty the vaginal secretion becomes distinctly acid and after the menstrual function is established the pH soon falls within the range of 4.0 to 5.0 in normal cases. This is approximately the range of the vaginal acidity which continues throughout the reproductive period until the menopause is approached.

During pregnancy there is a distinct tendency for the vaginal secretion to reach its maximum acidity: especially during the latter months when the estrogen level reaches its peak. The pH values during this period tend to approach pH 4.0 and occasionally reach as low as 3.8.

With the decrease in ovarian activity which occurs in the premenopausal phase there occurs a diminution in vaginal acidity. After the cessation of the menses the values tend to approach neutrality and not infrequently become alkaline, rarely, however, being more than pH 7.8.

*pH Changes in Association With the Menstrual Cycle.*—Rhythmic variations in vaginal acidity in association with the ovarian cycle have long been suggested but actually very few reliable data are available, probably because the range of variation throughout the cycle is small and the technical difficulties are great. As early as 1918 Gräfenberg<sup>15</sup> claimed to have demonstrated such rhythmic variations and stated that the acidity of the vagina diminishes from the early part of the cycle to the middle of the intermenstrual period when there is an interval of reduced acidity related to the rupture of the follicle. The acidity then rises to its highest level shortly before the next period. In their review of the subject, Oberst and Plass<sup>46</sup> point out that Heinlein<sup>47</sup> using the same technique was unable to detect regular cyclic changes in acidity but did note slight variations from day to day. Oberst and Plass<sup>46</sup> present some interesting data on cyclic variations in vaginal acidity in normal nonpregnant women and also in nonpregnant women with pathologic discharges based on pH readings of the vaginal discharge and also on total acidity obtained from titration values. Their data indicate that during the intermenstrual period the pH ranges from 4.0 to 4.5 but approaches or exceeds neutrality during the early days of menstrual bleeding; apparently, they were not able to note any significant variations in association with ovulation or other ovarian phases. Zuck and Duncan<sup>48</sup> on the other hand, obtained pH values of vaginal secretions which show not only a rhythmic variation with the menstrual cycle but also a characteristic rise at the time of ovulation. These data are not in apparent agreement with those of Rakoff<sup>10</sup> or of Guest<sup>24</sup> who find that the lowest values in normally menstruating women are obtained

during the ovulatory phase. It is to be pointed out, however, that the observations of Zuck and Duncan were made on mixed vaginal secretion and were no doubt influenced by the increase in alkaline cervical discharge which occurs at the time of ovulation. Our determinations were made directly on the vaginal mucosa, taking care to exclude contamination with cervical discharge.

*Vaginal pH as an Indicator of Ovarian Activity.*—It has already been pointed out that there is a marked difference in vaginal pH in different life phases due to variations in the ovarian function. Similarly, it has since been pointed out by a number of workers<sup>49, 50</sup> that pH determinations are also a useful indicator of diminished ovarian function and that these may also serve as one objective guide in treatment with estrogens. Only rarely are pH determinations of value in determining states of hyperestrogenism, since even with excessive concentrations of the hormone the readings do not usually fall below pH 4.0. Occasionally in pregnancy, values as low as 3.8 are encountered. In young women with so-called "hyperhormonal" leucorrhea, corresponding values have been encountered.

*Correlation of Vaginal pH and Vaginal Flora.*—Numerous observers have pointed out the relationship which exists between vaginal acidity and the type of vaginal flora, based upon the plan of recognizing three grades of bacterial flora: Grade I consisting of a homogeneous bacterial flora of Döderlein's bacilli; Grade II, Döderlein's bacilli plus other organisms; Grade III, organisms other than Döderlein's bacilli. Thus, Cruickshank and Sharman<sup>3</sup> make the following correlation:

GRADE	pH
I	4.0 to 4.4
II	4.6 to 5.6
III	5.6 to 7.6

Most workers feel that the range is not nearly so demarcated and that there is often considerable overlapping. Thus, on observations made by direct glass electrode readings of the middle vagina, Trussell and MacDougal<sup>51</sup> found the following values in late pregnancy:

GRADE	RANGE	AVERAGE
I	3.96 to 5.72	4.58
II	3.99 to 6.10	5.03
III	4.92 to 6.88	5.69

We have obtained strikingly similar results in a large group of non-pregnant patients (Table I).

A rather new note on this subject has been introduced by Weinstein and Howard<sup>52</sup> who question whether such a correlation exists at all. Their work is based upon studies made on menopausal women following injections with estrogenic hormone. They noted the usual fall in pH but could find no definite correlation between the degree of acidity of the vaginal secretions and the presence or absence of the Döderlein's

bacillus. Their findings support the clinical observations that low pH values are sometimes encountered even in the absence of Döderlein's bacilli, but this fails to alter the fact that in most *normal* women, normal pH values are commonly associated with a Grade I flora.

TABLE I. CORRELATION OF VAGINAL FLORA AND pH

	pH:	3.9 TO 4.5	4.6 TO 5.0	5.1 TO 5.5	5.6 TO 6.0	6.1 TO 6.5	6.6 TO 7.0	7.1 TO 8.0	8.1 TO 9.0	AVER- AGE
Grade I (210 patients)	%	52.4	34.3	9.5	3.8					4.56
Grade II (187 patients)	%	19.8	32.1	29.9	10.7	6.4	1.1			5.09
Grade III (323 patients)	%	9.3	17.4	33.1	24.1	9.3	5.3	0.6	0.9	5.54

### Observations on Vaginal pH

*Method.*—Until recently most determinations on vaginal acidity were made by one of the following methods: (1) collecting vaginal secretion and then determining the acidity by titration methods against various indicators; (2) by determining the concentration of lactic acid; (3) by measuring the pH of the fresh or diluted secretion; (4) indicator papers also have been employed for the rather rough measurement of vaginal pH. These methods have obvious disadvantages. It is often difficult to know from what part of the vagina the secretion originated and how much admixture there has been with cervical discharge; not infrequently, it is difficult to obtain a sufficient amount of material to make a reliable determination; some of the methods require dilution of the discharge which may also make an appreciable difference; also there is the possibility that the pH may change outside of the vagina as a result of evaporation, loss of CO<sub>2</sub>, and so forth. Trussell and MacDougal<sup>51</sup> made the suggestion that the pH of the vaginal mucosa itself could be determined by exposing the vagina and directly introducing the electrodes of a potentiometer. Trussell and MacDougal employed a glass electrode plus a capillary tube connecting with a calomel electrode. The advantages of this method are at once apparent. The pH may be obtained with a high degree of accuracy at any particular point in the vagina desired. The readings are obtained rapidly and conveniently and may be checked as frequently as is necessary. All of the technical difficulties of dealing with the secretion itself are avoided.

We have modified the electrode used by Trussell and MacDougal as shown in the accompanying figure (Fig. 9). The glass electrode has been made thinner and longer than the usual large electrode and the end has been curved to make it convenient to touch various portions of the vaginal wall. The calomel electrode is suspended in a container filled with a saturated solution of KCl. This is connected by rubber tubing with a thin, hard glass pipette bent to approximate the length and shape of the glass electrode so that it can be fitted snugly next to it with rubber



bands or a special holder. In this manner the two electrodes can then be introduced easily into the exposed vagina. Prior to its use a small amount of KCl solution is flushed through the tubing and a drop is permitted to collect at the point at which contact is made with the vagina. It is important to place the glass electrode at the exact point at which the reading is desired. Contact with the calomel electrode can be made at any neighboring point. In our setup the electrodes lead to a Beckman pH meter. When firm contact with the vaginal mucosa is

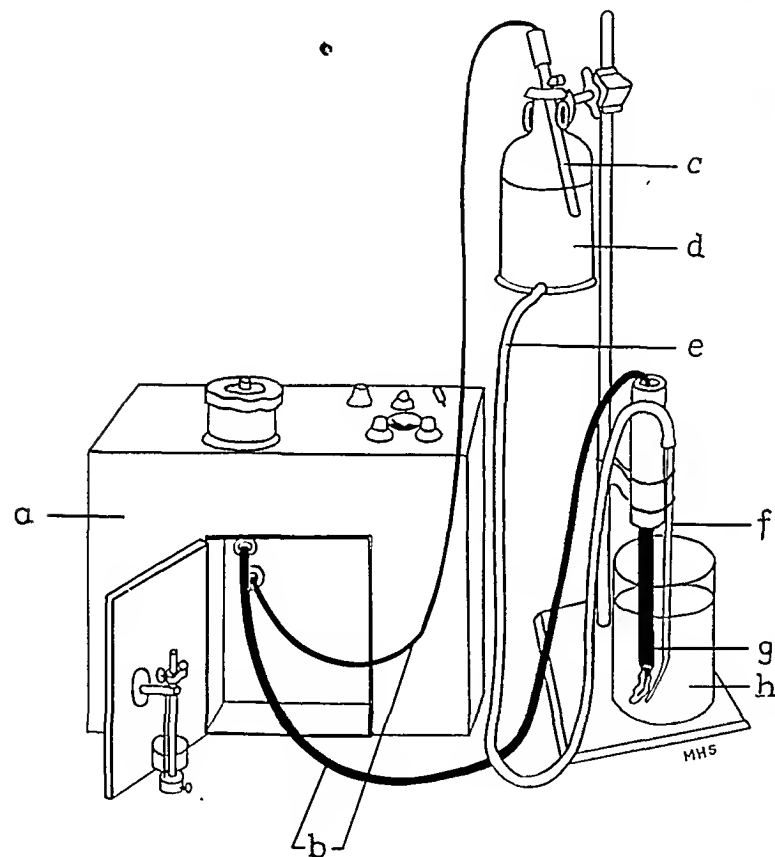


Fig. 9A.

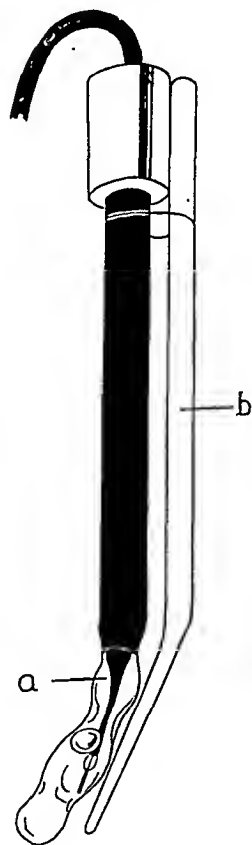


Fig. 9B.

Fig. 9A.—Shows setup employed in taking vaginal pH. (a) Beckman pH Meter, (b) leads to electrodes, (c) calomel electrode, (d) saturated solution of potassium chloride, (e) rubber tubing, (f) thick-walled glass tubing bent to fit snugly against glass electrode, (g) special glass electrode, (h) solution of bichloride of mercury 1:5,000 in which electrodes rest when not in use.

Fig. 9B.—Close-up of the vaginal electrodes (a) glass electrode made especially thin and curved for intravaginal use [length  $6\frac{1}{4}$  inches, thickness  $\frac{3}{8}$  inch], (b) thick-walled glass tubing bent to fit snugly against glass electrode; serves as an extension of the calomel electrode.

established the pH corrected for temperature may be obtained directly in a few seconds. After they have been used, the electrodes are carefully wiped in a solution of bichloride of mercury 1:5,000 and are permitted to rest in a beaker containing this solution until needed again.

As a routine, we have found it convenient to make readings of the vagina in the middle third of one of the lateral walls, in the anterior fornix, in the posterior fornix, and at the cervical os. For the latter

determination it is essential that the glass electrode fit directly into the os since otherwise the highest reading may not be obtained.

*pH Gradient of the Vagina.*—The highest pH readings (lowest acidity) are generally encountered in the lower third of the vagina (Fig. 10). The pH in the middle third of the vagina is considerably

### PH Gradient of the Normal Lower Genital Tract

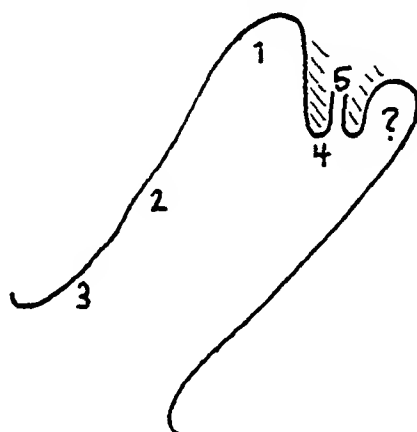


Fig. 10.—Highest readings are generally obtained in the anterior fornix (1); intermediate readings (usually the most constant) in the middle third of the vagina; (2) and lowest readings near the vaginal orifice. (3) The readings in the posterior fornix are rather inconstant because of the presence of cervical discharge. Higher pH readings are obtained at the cervical orifice; (4) and these may approach or exceed neutrality within the cervical canal. (5) The special vaginal electrodes may be obtained from Arthur H. Thomas & Co., Philadelphia, Pa.

### Average Mid-Vaginal pH in 37 Normally Menstruating Women



Fig. 11.—Average pH readings in 632 readings made on 37 normally menstruating patients.

lower and usually the most constant and, as a rule, gives values quite similar to those obtained from mixed vaginal secretion. In our experience, the lowest pH values are obtained in the anterior fornix. The readings in the posterior fornix are strongly influenced by the amount of cervical discharge which has collected here: if but little of this is

present the pH of the posterior fornix may be almost identical with that of the anterior fornix, but more often because some contamination with cervical discharge has occurred, it approaches that of the mid-vagina. In those instances in which a profuse cervical discharge is present, the acidity is usually markedly reduced.

*Cyclic Variations of pH in Normal Women.*—We have collected a total of 632 readings of the midvaginal pH at various periods of the menstrual cycle on 100 women in whom all other vaginal factors were normal (Fig. 11). In all determinations save 19 instances (3 per cent), the range of the pH varied between 4.0 and 5.0. In 2 recordings a pH of 3.9 was obtained, while in 17 other instances the range was found to be 5.1 to 5.6. (In a number of the latter cases we have reason to believe that the higher pH values may have been influenced by recent coitus or douching.) Based on these findings, it would appear that for all practical purposes the normal pH range of the midvagina throughout the cycle lies between 4.0 and 5.0. It is to be pointed out that these values do not include readings taken during menstruation since during this phase considerably higher pH readings may be obtained because of contamination with the alkaline blood. We have found, however, that if the blood is carefully wiped away, the readings are quite commonly in the neighborhood of pH 5.0.

In 37 cases in which we have obtained a sufficient number of readings during several cycles, there is evidence of a periodic variation of pH (Fig. 11). If average determinations are made based on the number of days before the next menses, it will be noted that the pH is highest in the early days of the cycle and that it gradually falls to reach the lowest values in the midcycle. This high degree of acidity is maintained through most of the luteal phase but gradually tends to rise in the premenstrual phase.

In a number of patients, we made daily pH determinations during the intermenstrual period along with vaginal smears and basal rectal temperatures in order to determine whether there was any sharp variation in association with the ovulatory type of smear. Except for the gradual decline noted, we were not able to determine any significant sharp change in midvaginal pH. In several instances, however, there was a very decided increase in the pH at the cervical os. This may be related to the increase of the cervical discharge which has been associated with ovulation.<sup>52</sup>

The readings in some of the cases studied were quite erratic and it was not possible to demonstrate any significant fall at the midcycle. This may be attributed to certain factors:

1. It is well known that some normally menstruating women may have irregular excretion of the gonadal hormones. These may be the patients in whom the most irregular values were obtained.

2. In some of the patients anovulatory cycles may have been present. In this respect it might be pointed out that in a few of the cases studied, the midvaginal pH remained quite constant from day to day.
3. It is acknowledged that an insufficient number of readings may have been made during each cycle, and therefore, transitory changes may not have been detected.

#### IV. Vaginal Flora

It is well recognized that the biochemical factors present in the vagina are capable of determining to a considerable extent the character of its bacterial flora. Thus, the organisms within the vagina are considerably different from those found on the vulva and frequently different from those found in the cervix proper. Moreover, the vaginal flora changes in the various life phases just as do the other biologic factors which have been discussed.

*Vaginal Flora in Various Periods of Life.*—At birth the vagina is sterile. Organisms make their appearance in 12 to 24 hours<sup>3</sup> and at first consist of a small number of such organisms as staphylococci, enterococci, and diphtheroids. But as early as the second or third day, these are commonly replaced by a practically pure culture of lactobacilli (Döderlein's bacilli<sup>4</sup>). It is supposed by some that the latter organisms originate by contamination from the feces as soon as the lactobacilli become established in the intestinal tract of the newborn; but this is a mooted question. The important factor is that within a few days, a distinctive bacterial flora becomes established in the vaginal tract of the infant and is maintained so long as the biochemical factors remain under the influence of the estrogens, derived from the maternal circulation. Within a week or ten days when the latter has been completely excreted, Döderlein's bacilli are in turn replaced by a varied flora of staphylococci, nonhemolytic streptococci and coliform and diphtheroid bacilli. This is a striking clinical experiment illustrating the influence of estrogens in determining the vaginal flora. The mixed bacterial flora persists until puberty. Shortly before or soon after the menarche, Döderlein's bacillus reappears, and as the ovarian function becomes well established, it tends to become the predominant organism in the vaginal tract. During the period of sexual maturity the vaginal flora may consist of Döderlein's bacilli alone, or may be associated with the organisms already mentioned as well as with anaerobic streptococci which appear to be commonly present in the female genital tract.<sup>53</sup> Under unfavorable circumstances Döderlein's bacilli may disappear completely and be replaced by some other organism, but more commonly by a variety of bacteria, usually saprophytes, but occasionally pathogens may also be present. This concept is the basis for the simple classification of Schröder.<sup>54</sup>

- Grade I: Consists of Döderlein's bacilli only.  
Grade II: Consists of Döderlein's bacilli and other organisms.  
Grade III: Consists of organisms other than Döderlein's bacilli.

This classification of flora has long been accepted also as an index of the normality or state of cleanliness (Reinheitsgrade) of the vagina in which the Grade I flora is accepted as normal and the Grade III as the most abnormal.

During pregnancy when the maternal organism is surfeited with estrogens, conditions appear to be particularly favorable for the lactobacilli and it has been shown by many studies that as pregnancy progresses the proportion of patients with a Grade I flora increases. Following parturition and for a varying length of time during the puerperium, the vaginal flora resembles that of the vulva, not merely because of the rapid decline in estrogenic hormone, but also because of the inhibiting influence of the alkaline lochia and the trauma incident to labor.

In the years of diminished ovarian function which come with the menopause and thereafter, the vaginal flora gradually reverts to the childhood type, although it cannot be denied that a small proportion of postmenopausal women may harbor Döderlein's bacilli for many years, just as many postmenopausal women retain some minimal ovarian function for many years.

*What Is the Normal Vaginal Flora?*—It has already been intimated that the character of the vaginal flora is determined largely by the underlying mechanism upon which the physiologic factors in the vagina are based; namely, ovarian activity, glycogen deposition and pH. Since, under normal circumstances, glycogen content and acidity are influenced by the degree of ovarian function, it is reasonable to expect the vaginal flora to vary with the various life phases associated with changes in ovarian function. As has already been pointed out, through most of childhood and in the postmenopausal period when there is but little ovarian function the vaginal flora is varied, whereas during the sexually mature period of life a homogeneous flora of lactobacilli tends to become established. On the other hand, it cannot be denied that there are a small percentage of clinically normal cases in which the various physiologic characteristics also appear to be within the normal range and yet organisms other than Döderlein's bacilli are present. Also, the converse is not infrequently true; mainly, that patients with evidences of decreased ovarian function and decreased acidity may harbor the lactobacilli. This is graphically illustrated in Table I in which the mid-vaginal pH of patients is plotted against the grade of flora.

From these observations it is apparent that although the presence of a Grade I flora may be a good indicator that the vagina is clinically normal, it does not necessarily mean that it is physiologically normal, although there is a strong probability that it is.

From the data which are available, it appears that inhabitation of the vagina by the lactobacilli is dependent mainly, if not entirely, upon the degree of acidity. Apparently, there are but few organisms which, having an opportunity to enter the normal vagina, can survive and flourish in an environment of pH 4.0 to 4.5. Not infrequently, certain yeasts may do this; certain yeast-like fungi also appear to be favored by such an environment, but the latter cannot be considered normal since they often produce an inflammatory lesion of the vagina and vulva. Next to these, certain aciduric streptococci (*Streptococcus fecalis*) and certain strains of diphtheroids are able to tolerate moderate degrees of acidity.

For purposes of definition and also in the selection of patients with normal vaginas for study, it is our belief that the normal vaginal tract is one in which not only the histologic and biologic characteristics are within normal but in which a homogeneous flora of lactobacilli are present.

*Döderlein's bacillus.*—The first comprehensive description of this organism appeared in a classic monograph of Döderlein on the vaginal flora. Since then, numerous observations but very few extensive studies concerning this organism have been made. Our present knowledge of this organism may be summarized as follows:

*Morphologic Characteristics.*—As seen in vaginal smears, Döderlein's bacillus most commonly appears as a rather long gram-positive rod of moderate thickness, often slightly curved with ends which tend to be rounded. This organism, however, is capable of considerable pleomorphism and a number of subspecies have been described based on morphologic variations.<sup>41</sup> The more common morphologic variants are: (1) a short, thick, blunt rod usually appearing singly; (2) an elongated, thin rod 2 to 3 times the length of the usual form and often distinctly wavy in appearance; (3) a very short rod, almost a coccobacillus which very frequently appears in diploid formation and can easily be mistaken for diphtheroids or enterococci.

*Cultural Characteristics.*—From its general cultural characteristics this organism has been classified as a member of the lactobacilli. The organism is rather fastidious in its cultural requirements and does not grow well on ordinary media. Among the special media most suitable for its growth are whey-agar, tomato juice agar or broth, and particularly the tomato-milk medium of Weinstein et al.<sup>55</sup>

The colony and cultural characteristics of Döderlein's bacillus and *Lactobacillus acidophilus* have been shown to be very similar<sup>56</sup> so that differentiation cannot be made on these grounds. It was shown by these same workers that Döderlein's bacillus is serologically different from *L. acidophilus* and in fact, several strains of Döderlein's bacilli differed from each other serologically.

*Other Organisms Found in the Normal Vagina.*—It is well recognized that the apparently normal vagina may harbor a variety of organisms. Even in those instances in which vaginal smears show a uniform Grade I flora, other organisms can be obtained by cultural methods, particularly,

if a number of culture media suited to the growth of different types of organisms is employed. Among the more common inhabitants of the vaginal tract are certain staphylococci, streptococci, diphtheroids, and coliform organisms. Their presence in only small numbers in the normal vagina is very likely due to inhibition of growth by the high degree of acidity. It is probable that some of the simpler sugars in the vagina may be broken down by these organisms and some initial degree of acidity produced, which in turn is inimical to their further growth.<sup>31</sup> Their significance, however, lies in the fact that as soon as the normal protective mechanism is interfered with, either by physiologic or external factors, their growth will be greatly accelerated.

Special mention should be made of the yeast and yeast-like organisms which are so commonly found in the normal vagina. The growth of these organisms is favored by a high degree of vaginal acidity and the presence of fermentable carbohydrates in the vaginal secretion. Therefore, it is not surprising that they are most commonly found in the normal vagina usually associated with Döderlein's bacilli alone. Indeed, they tend to occur most frequently in pregnancy since, in the latter state the acidity and carbohydrate factors are most favorable.

### Summary

1. Extensive studies were made on the vaginal tract of more than 500 patients; included in this number were 37 normal patients in whom the studies were made three times weekly through one to three menstrual cycles. The special studies made included determinations of the pH of the vaginal mucosa, cytologic studies of vaginal smears, examination of smears stained for glycogen content, determination of the bacterial flora, and the study of vaginal biopsies.

2. The role of the estrogens as the major factor in controlling the histologic and cytologic features of the vaginal epithelium is reviewed, but evidence indicating that progesterone and perhaps other steroid hormones have an important influence is presented. Certain cyclic histologic changes were frequently noted on the biopsies, but in the main these were not nearly so clear-cut as the changes noted from cytologic study of vaginal smears.

3. Present evidence indicates that the estrogens are the dominant factor in causing the mobilization of glycogen in the vaginal epithelium; progesterone may aid in this process. Androgens appear to be an inhibiting factor in glycogenesis.

Glycogen is abundantly present in vaginal biopsies. A concentration of 2.5 to 3.0 mg. per cent was encountered in the upper part of the vagina and smaller concentrations in the lower part of the vagina. The metabolism of vaginal glycogen is not known, but various theories are discussed.

Vaginal biopsies prepared with Best's carmine stain were found to be highly suitable for demonstrating distribution of vaginal mucosa. Cyclic changes in glycogen content were far more easily noted in vaginal smears stained by an iodine method. It was found that the glycogen content of the superficial vaginal epithelium showed a tendency to increase throughout the cycle and then to fall in the late premenstrual phase, thus roughly approximating the estrogen excretion through the cycle.

4. The various methods for determining the pH of the vaginal secretion and mucosa are reviewed. Direct determination of the pH of the vaginal mucosa by the glass electrode method was chosen as most accurate and reliable. A special glass electrode is described which has been found to be highly satisfactory for this purpose.

In making 632 readings on 100 normal women, it was found that the pH varied from 4.0 to 5.0 in all except 3 per cent of the determinations.

A pH gradient was found to exist in the vagina in most patients. The highest acidity was generally encountered in the anterior fornix. The next highest readings were obtained in the middle third of the vagina; these were generally quite constant and most nearly approximated the pH of the vaginal secretion. Lower values were obtained in the lower third of the vagina, while determinations made in the posterior fornix usually varied considerably. In the 37 cases studied at frequent intervals, a periodic variation in pH was observed in many instances. The average readings indicate that pH gradually falls to reach its lowest point at the midcycle and then gradually rises to meet the highest values at the premenstrual stage.

5. The factors which influence the character of the vaginal flora are discussed. From available evidence it would appear that the vaginal pH is the strongest immediate factor determining the type of organisms present in the vaginal tract.

The vaginal pH and flora were correlated for a large series of patients and indicated that most of the patients with Grade I flora had a vaginal pH of 3.9 to 5.0 (range 3.9 to 6.0, average 4.56). Majority of patients with a Grade II flora fell in the pH interval 4.6 to 5.5 (range 4.0 to 7.0, average 5.09). In Grade III type the majority of the patients had a pH of 5.1 to 6.0 (range 4.0 to 9.0, average 5.54).

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## ACUTE ANTERIOR POLIOMYELITIS DURING PREGNANCY\*

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**A**CUTE paralytic anterior poliomyelitis has been observed as a complication of human pregnancy. This observation raises several questions: (1) Does pregnancy per se affect the susceptibility of the mother to the disease? (2) Is the disease transmissible from mother to fetus in utero? (3) Is the disease transmissible to the offspring through the secretions of the mammary glands? To our knowledge the problems presented by these questions have not been investigated experimentally. The present communication records experiments and results pertinent to these problems.

### Part I. Effect of Pregnancy Per se on Susceptibility of the Mother

A total of 75 cases diagnosed as paralytic anterior poliomyelitis acquired during pregnancy† have appeared in the literature (cases cited in Table I). Since the majority of these cases have been reported within the last few years, it may be that the small number of cases is due to incomplete reporting rather than to a rarity of this condition as indicated by the work of Aycock (1941). In 5 of the reported cases the records are so incomplete as to be of little value. Of the remaining 70 cases, one or more has been recorded for each month of the gestation period. Of these, 17.1 per cent occurred during the first trimester, 34.3 per cent during the second trimester, and 48.6 per cent during the third trimester.

*Experimental Method.*—A 10 per cent, unfiltered suspension of the virus of poliomyelitis was made from the glycerolated brain stems and spinal cords of cotton rats paralyzed by treatment with the Armstrong-Lansing strain. Each of the cotton rats in this experiment was given a single three-way inoculation (0.1 c.c. intracerebral, 0.5 e.e. subcutaneous, 0.1 e.c. intranasal) with the virus (see Table II).

Sixty-four cotton rats of comparable ages were used in this experiment. For convenience, the 28-day gestation period of these animals was divided into trimesters for the purpose of comparing the relative susceptibility at different stages of pregnancy. Three groups of animals have been observed. Group 1 includes the pregnant animals‡ with

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†One case was reported by Foulkrod (1923) but, as McGoogan (1932) has already indicated, this was probably not a case of poliomyelitis. Aycock (1941) cited a case supposed to have been reported by Guttman (1932) as one of poliomyelitis. A review of Guttman's report indicates that this was a case of uncomplicated apical poisoning rather than of anterior poliomyelitis. Another case was reported by Peelen (1943) as having occurred in the fourth month of pregnancy. The evidence presented, however, does not justify including this case as one of anterior poliomyelitis.

‡We are indebted to Dr. C. C. Young and his staff of the Michigan Department of Health Laboratories, Lansing, Mich., for supplying the timed-pregnancy cotton rats used in this investigation.

TABLE I

CASE NUM- BER	AUTHOR AND YEAR	MONTH OF PREGNANCY	AGE OF MOTHER	PARALYTIC INVOLVEMENT
1	Schell, 1906	7	26	Lower extremities
2	Hartman, 1909*	4	?	?
3	Hartman, 1909*	7	?	?
4	Hartman, 1909*	7	?	?
5	Hartman, 1909*	8	?	?
6	Hartman, 1909*	8	?	?
7	Hartman, 1909*	9	?	?
8	Mueller, 1910	9	?	?
9	Mueller, 1910	9	?	?
10	Renault and Martingay, 1911	5	23	Lower extremities and abdo- men
11	Wickman, 1913	?	?	?
12	Zimmermann, 1914	9	22	All extremities, abdomen, and back
13	Miller, 1924	3	26	Lower extremities
14	Miller, 1924	6 ?	?	Left lower extremity, bladder, and rectum
15	Hornung and Creutz- feldt, 1930	9	?	Landry's ascending type with respiratory involvement
16	McGoogan, 1932	3	24	Right lower extremity
17	McGoogan, 1932	3	24	Both lower and right upper ex- tremities
18	McGoogan, 1932	3	32	Lower extremities and abdo- men
19	Brahdy and Lenarsky, 1933	2	19	Lower extremities, abdomen, and back
20	Brahdy and Lenarsky, 1933	4	23	Right lower extremity
21	Brahdy and Lenarsky, 1933	9	22	Lower extremities
22	Ehrenfest, 1933	7	18	Right lower and upper extremi- ties and face
23	Pette, 1936	3	?	Death due to respiratory in- volvement
24	Fischer and Stillerman, 1937	8	?	Lower extremities and abdo- men
25	Klein and Sittig, 1938	9	25	All extremities
26	Ruhl, 1939	9	27	All extremities, abdomen and back with respiratory and deglutition involvement
27	Morrow, Luria and Ridgewood, 1939	5	28	All extremities, abdomen, blad- der and rectum
28	Author unknown,† 1939	7	18	Respiratory involvement
29	Spishakoff, Golenterneck and Bower, 1941	8	22	All extremities with respira- tory involvement
30	Helms, 1941	5	35	Lower extremities and abdo- men
31	Helms, 1941	6	18	Left lower extremity and ab- domen and flexors of head
32	Helms, 1941	6	29	Right upper extremity
33	Helms, 1941	8	21	Both lower and left upper ex- tremities, abdomen and back

TABLE I—CONT'D

CASE NUM- BER	AUTHOR AND YEAR	MONTH OF PREGNANCY	AGE OF MOTHER	PARALYTIC INVOLVEMENT
34	Helms, 1941	9	36	Upper extremities, abdomen, back, and neck
35	Aycock, 1941	?	?	?
36	Aycock, 1941	?	?	?
37	Aycock, 1941	1	26	?
38	Aycock, 1941	2	Young	?
39	Aycock, 1941	3	24	?
40	Aycock, 1941	4	20	?
41	Aycock, 1941	4	30	?
42	Aycock, 1941	4-5	16	?
43	Aycock, 1941	5	19	?
44	Aycock, 1941	5	24	?
45	Aycock, 1941	5	27	?
46	Aycock, 1941	5	33	?
47	Aycock, 1941	6	?	?
48	Aycock, 1941	6	?	?
49	Aycock, 1941	6	16	?
50	Aycock, 1941	6	20	?
51	Aycock, 1941	6	35	?
52	Aycock, 1941	7	23	Death due to respiratory in- volvement
53	Aycock, 1941	7	25	?
54	Aycock, 1941	7	26	?
55	Aycock, 1941	7	26	?
56	Aycock, 1941	7	32	?
57	Aycock, 1941	8	26	?
58	Aycock, 1941	9	?	?
59	Aycock, 1941	9	22	Respiratory involvement
60	Aycock, 1941	9	23	?
61	Gillespie, 1941	7	18	Landry's ascending type
62	Newberger and Associ- ates†	9	22	Lower extremities, abdomen with respiratory paralysis
63	Kleinberg and Horwitz‡	?	18	All extremities, abdomen, back, and vocal cords
64	Kleinberg and Horwitz‡	?	26	All extremities
65	Kleinberg and Horwitz‡	2	24	Lower extremities
66	Kleinberg and Horwitz‡	3	24	Lower extremities, abdomen and bladder
67	Kleinberg and Horwitz‡	3	26	Lower extremities, abdomen, back and bladder
68	Kleinberg and Horwitz‡	4	19	Right lower extremity
69	Kleinberg and Horwitz‡	4	25	Lower extremities
70	Kleinberg and Horwitz‡	6	24	All extremities
71	Kleinberg and Horwitz‡	6	28	Right lower extremity
72	Kleinberg and Horwitz‡	7	?	Left lower extremity and ab- domen
73	Kleinberg and Horwitz‡	7	17	Left lower extremity
74	Kleinberg and Horwitz‡	7	21	Both lower and right upper extremities
75	Peelen, 1943	9	29	Both lower and left upper ex- tremities

\*Cited by Aycock, 1941.

†München. med. Wchnschr. 86: 160, 1939.

‡Personal communication from Kleinberg and Horwitz, 1942.

viable fetuses and those which had delivered viable young within twenty-four hours. Group 2 includes animals whose fetuses had been resorbed (autopsy). Group 3 includes virgin female cotton rats as controls.

*Results.*—As set out in Table II, the average incubation period and extent of paralysis in each of the three groups is not significantly different. This conclusion is justifiable in view of the fact that the incubation period and extent of paralysis of the individual animals in any one group show a wide variation.

It is of interest to note that the only animals which developed no symptoms of poliomyelitis were 3 out of 13 animals inoculated with the virus during the first trimester of pregnancy.

TABLE II

	NO. OF ANI- MALS	TIME OF INOCULATION	INCUBA- TION PERIOD (DAYS)	EXTENT OF PARALYSIS (EXTREMITIES)	NO. OF ANIMALS RESIST- ANT TO INOCULUM
Group 1	7	During first trimester	3.66 (2- 6)	3.66 (2-4)	1*
Pregnant cot- ton rats with viable fetuses	5	During second trimester	6.40 (3-10)	3.20 (2-4)	0
	6	During third trimester	4.66 (3- 6)	3.66 (2-4)	0
	6	Within 24 hrs. post partum	6.33 (3-13)	4.00	0
Summary Group 1	24		5.22 (2-13)	3.78 (2-4)	1*
Group 2	6	During first trimester	6.25 (5- 8)	3.50 (2-4)	2†
Pregnant cot- ton rats with re- sorbed fetuses	8	During second trimester	4.88 (2- 9)	3.25 (2-4)	0
	2	During third trimester	6.00 (5- 7)	4.00	0
Summary Group 2	16		5.43 (2- 9)	3.43 (2-4)	2†
Group 3 Virgin female cotton rats	24		6.58 (3-12)	3.42 (2-4)	0

\*When subjected to a second three-way inoculation 20 days after the first, and a few hours after giving birth to her young, this animal became completely paralyzed following an incubation period of eleven days.

†These animals became completely paralyzed following a single three-way inoculation administered in one case fourteen days and in the other case twenty-one days after their first exposure to the virus.

## Part II. Intrauterine Transmissibility of the Virus

In the human being 6 cases which were regarded as prenatal anterior poliomyelitis have been collected from the literature (Lamy, 1894; McCarthy, 1907-1908; Fritsch, 1908; Batten, 1910-1911; and Potts, 1929). The diagnosis of anterior poliomyelitis (Heine-Medin's disease) in these 6 cases is highly questionable for the following reasons: (1) No disease resembling anterior poliomyelitis was diagnosed in the mother during the prenatal period of any of these cases. (2) The virus of poliomyelitis was never recovered from the excreta or from the tissues out of any of these cases nor from the mothers of any of these cases. (3) Several of these cases were diagnosed as anterior poliomyelitis only after they were well advanced in years and long after the acute stage of any such disease had subsided. (4) In none of these reports was it stated that an epidemic of poliomyelitis was prevalent in the community during the prenatal period of any of the 6 cases. In addition, it should be pointed out that a review of 75 cases of paralytic poliomyelitis ac-

quired during pregnancy (see Table I) failed to reveal a single instance in which a paralyzed mother gave birth to a child who developed clinical signs of poliomyelitis.

*Experimental.*—The fetuses from 15 cotton rats paralyzed following a three-way inoculation with the Armstrong-Lansing strain of the virus of poliomyelitis, were removed from the fetal membranes as rapidly as possible after the death of the mother (see Table III). The central nervous systems of the fetuses in each litter were made into a 10 per cent suspension with normal saline.\* Each of these suspensions were inoculated in the usual three-way manner into 2 or 3 previously untreated cotton rats. Of 31 animals so inoculated, 5 only were sacrificed because of clinical manifestations occurring within a period of time equal to the usual incubation period of the virus. Of these 5 animals, 2 only appeared to be clinically paralyzed. In no case were clinical manifestations exhibited by more than 1 out of the 2 or 3 cotton rats treated with the same inoculum. Microscopic sections from samples of the central nervous systems of the 5 animals which had exhibited clinical manifestations revealed no histopathologic changes suggestive of anterior poliomyelitis.

A further passage into previously untreated cotton rats was attempted from each of 4 out of the 5 animals which had exhibited clinical manifestations. This was accomplished by making a 10 per cent suspension of the central nervous system from each animal (small bits of tissue had been utilized for microscopic examination). Each of these suspensions were inoculated in the usual three-way manner into 2 or 3 previously untreated cotton rats (see Table III). Of 9 animals so treated, 1 only died. This animal exhibited no symptoms whatsoever of anterior poliomyelitis, and examination of serial sections from the entire central nervous system of this cotton rat revealed no evidence of the disease.

### Part III. Transmissibility of the Virus Through Mammary Secretions

Two mother cotton rats were inoculated with the virus of poliomyelitis in the usual three-way manner 24 hours after they had given birth to their young. The offspring remained with and received nourishment from their mothers until the latter expired with poliomyelitis. In the first case the mother lived for 8 days and in the second case for 11 days after the young were born. Each mother appeared to satisfy the nutritional demands of her offspring until about 48 hours prior to her death. Artificial feeding of the offspring was successful and they grew normally and without loss. The first litter consisted of 2 males and the second of 4 males and 2 females. None of the offspring showed any evidence of paralysis, nor did any of these animals show any resistance to intracerebral inoculations with potent suspensions of the virus administered 25 days after the death of the mother.

### Discussion

It is conceivable that during pregnancy an altered susceptibility to paralytic anterior poliomyelitis might result from an alteration in the permeability of the portal of entry of the virus and/or a change in the effective "internal resistance" (neutralizing substance, circulating virucidal substances, etc.) of the host. The fact that certain hormones

\*One fetus from each of 6 mothers paralyzed with poliomyelitis was preserved in formalin and prepared for histologic study. The microscopic sections revealed no histopathologic changes suggestive of poliomyelitis in the central nervous systems of any of these 6 fetuses.

1 FETUS NUMBER	2 MOTHER INOCULATED (DAY OF PREGNANCY)	3 MOTHER SACRIFICED (DAY OF PREGNANCY)	4 EXTENT OF MOTHER'S PARALYSIS	5 HISTOPATHOLOGY CNS OF FETUSES SEE COLUMN 1	6 ATTEMPTED PASSAGE FROM CNS OF FETUSES SEE COLUMN 1		7 HISTOPATHOLOGY CNS OF FIRST-PASSAGE ANIMALS SEE COLUMN 6
					NUMBER OF ANIMALS INOCULATED	RESULTS	
436	2nd	4th*	1, 2, 3, 4 plegia†		2	Both negative	
791	7th	9th	1, 2, 3, 4 plegia		2	<div> 1 negative  1 apparently completely paralyzed </div>	
1023	4th	10th	1, 2 plegia		2	Both negative	
1020	7th	12th	1, 2, 3, 4 plegia		2	Both negative	
457	8th	12th	1, 2, 3, 4 plegia		2	Both negative	
456	11th	14th	1, 2 plegia		2	<div> 1 negative  1 expired without paralysis </div>	Negative
939	14th	19th	1, 2, 3, 4 plegia	Negative	2	<div> 1 negative  1 expired without paralysis </div>	Negative
1305	14th	20th	2, 3 plegia	Negative	2	Both negative	
940	14th	22nd	1, 2, 3, 4 plegia	Negative	2	Both negative	
943	14th	24th	1, 2, 3, 4 plegia	Negative	2	Both negative	
573	19th	25th	1, 2, 3, 4 plegia		2	Both negative	
621	21st	26th	1, 2, 3, 4 plegia	Negative	2	Both negative	
622	22nd	27th	3, 4 plegia	Negative	2	Both negative	
320	24th	28th	1, 2, 3, 4 plegia		2	<div> 1 negative  1 apparently completely paralyzed </div>	Moderate gliosis
300	24th	29th	1, 2, 3, 4 plegia		3	<div> 2 negative  1 expired without paralysis </div>	Negative

\*Expired.

†1 plegia = flaccid paralysis of left front extremity.

2 plegia = flaccid paralysis of right front extremity.

III

8 RESULTS OF INOCULATING VIRULENT VIRUS INTO SURVIVING FIRST-PASSAGE ANIMALS SEE COLUMN 6	9 ATTEMPTED FURTHER PASSAGE FROM CNS OF QUESTIONABLY POSITIVE FIRST-PASSAGE ANIMALS SEE COLUMN 6		10 HISTOPATHOLOGY CNS OF SECOND-PASSAGE ANIMALS SEE COLUMN 9	11 RESULTS OF INOCULATING VIRULENT VIRUS INTO SURVIVING SECOND- PASSAGE ANIMALS SEE COLUMN 9
	NUMBER OF ANIMALS INOCULATED	RESULTS		
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
1 paralyzed after 1st re- inoculation	2	Both negative		{ 1 paralyzed after 1st reinoculation 1 paralyzed after 2nd reinoculation
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
1 paralyzed after 1st re- inoculation	2	Both negative		Both paralyzed after 1st reinoculation
1 paralyzed after 1st re- inoculation				
Both paralyzed after 1st reinoculation				
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
Both paralyzed after 1st reinoculation				
{ 1 paralyzed after 1st re- inoculation 1 resisted 3 reinoculations				
Both paralyzed after 1st reinoculation				
Both paralyzed after 1st reinoculation				
1 paralyzed after 1st re- inoculation	3	{ 2 negative 1 expired without paralysis	Negative	Both paralyzed after 1st reinoculation
2 paralyzed after 1st re- inoculation	2	Both negative		Both paralyzed after 1st reinoculation

1, 2, 3, 4 plegia = complete flaccid paralysis.

3 plegia = flaccid paralysis of right rear extremity.

4 plegia = flaccid paralysis of left rear extremity.



are present in increased amounts during pregnancy has stimulated a number of workers to speculate as to the relation of the endocrine glands to the occurrence of paralytic anterior poliomyelitis. In the human being pregnancy is characterized by an elevation in the levels of two hormones, estrogen and progesterone, which are present in normal individuals; and the addition of an entirely new substance, gonadotropin.

It has been said that the quantity of urinary estrogen (presumably an index of estrogen formation) in the human being rises at an increasing rate until parturition, after which it disappears in the course of a few days (Newton, 1939). At term, the total estrogenic substance excreted in the urine may be in amounts as high as 100,000 rat units daily (Freed, 1942).

The investigations of Aycock (1937-1940) indicate that the permeability of the nasal mucosa to the virus of poliomyelitis can be altered by preliminary treatment with estrogen. Schultz (1941) was unable to corroborate these findings. The studies of Jungeblut and his co-workers (1934) and Clark (1941) indicate that there is no apparent relationship between estrogen and the effective "internal resistance" of the host as judged by the occurrence of neutralizing bodies in the serum and resistance to intracerebral inoculations with the virus.

Urinary progesterone, excreted mainly as pregnandiol glucuronide, begins to rise during the first month of pregnancy and in the ninth month may have a value exceeding ten times that found in the luteal phase of the menstrual cycle (Newton, 1939). To our knowledge, the possible relationship of progesterone to the resistance of an individual to the virus of poliomyelitis has never been investigated.

Chronic gonadotropin (anterior pituitary-like hormone) appears in the urine of the pregnant woman within a few days after the first missed period. From twenty to fifty days after the missed period, tremendous quantities of this substance are present in the urine. Several hundred thousand rat units have been demonstrated to be present in one liter of urine obtained from a pregnant woman during this interval of time (Evans, Kohls, and Wonder, 1937). After this time the daily excretion remains at a fairly constant level, from 3,000 to 10,000 rat units, until termination of pregnancy, after which it disappears normally within four or five days (Freed, 1942).

Jungeblut and his co-workers (1934) stated that they were able regularly to neutralize the virus of poliomyelitis *in vitro* with sera from two pregnant mares obtained during the second trimester, and irregular results were obtained with crude prolactin. The serum from pregnant mares obtained between the fiftieth and one hundred fiftieth days of pregnancy is known to contain large quantities of chorionic gonadotropin, whereas crude prolactin used by Jungeblut probably contained a much smaller quantity of this substance.

Jungeblut and Engle (1934) subjected 23 immature rhesus monkeys to daily injections of 2 to 8 c.c. of prolan for from 9 to 30 days. Fifteen of twenty-nine samples of serum obtained from these animals after treatment with prolan neutralized either partially or completely, the virus of poliomyelitis in vitro. Four of these animals either resisted completely an intracerebral inoculation with the virus of poliomyelitis or contracted the disease only after a prolonged incubation period.

A review of the literature (Table I) reveals that of the cases of paralytic poliomyelitis in the human being which were contracted during pregnancy, only 17.1 per cent occurred within the first trimester. It is during this third trimester of pregnancy in the human being that the formation of chorionic gonadotropin is at its peak.

In this connection, it is of interest to note that the only pregnant cotton rats of our group resistant to the first inoculation with the virus of poliomyelitis were three which were inoculated between the fourth and seventh days of pregnancy. Although we have no information relative to the formation of chorionic gonadotropin during pregnancy in the cotton rat, from studies on other species it is probable that, if it is formed at all, its production may reach a peak near the time these animals were inoculated. That these animals were temporarily resistant to the inoculum only is demonstrated by the fact that each became completely paralyzed following a second three-way inoculation with the virus of poliomyelitis administered between 14 and 21 days later. It is probable that chorionic gonadotropin was not present in significant quantities in these animals at the time of the second inoculation, since one rat had delivered her young and the other two animals had resorbed their fetuses. The incubation period following the second inoculation with the virus was within normal limits.

We do not believe it to be an accident of experimentation that 3 out of 13 cotton rats inoculated during the first trimester of pregnancy were resistant to their first exposure to the virus of poliomyelitis. During the past two years we have subjected over 300 previously untreated and nonpregnant cotton rats of all ages to three-way inoculations with the Armstrong-Lansing strain of the virus of poliomyelitis. Of these, 2.86 per cent of the males and 2.53 per cent of the females resisted their first exposure to the virus and succumbed, completely or partially paralyzed, to a second three-way inoculation. In contrast to these figures, 23.08 per cent of the pregnant cotton rats inoculated during the first trimester of pregnancy resisted the virus.

It would appear from the information at hand, that chorionic gonadotropin, or some substance associated with the formation or metabolism of this hormone, might play a role in increasing the resistance of the pregnant female during the first trimester of pregnancy to the virus of poliomyelitis. It should be emphasized, however, that this possibility is suggestive only. The greater number of cases of the disease

in the human being acquired during the latter months of gestation might result from the diminished secretion of chorionic gonadotropin or might be due entirely to other factors peculiar to the latter months of pregnancy.

We believe that the experiments reported earlier in this communication indicate that in the cotton rat infective quantities of the Armstrong-Lansing strain of the virus of poliomyelitis are not transmitted from a mother to the nervous tissues of a fetus in utero. It appears further that the virus is not transmissible to the offspring through the secretions of the mammary glands. These findings were not unexpected in view of the fact that an overwhelming majority of attempts to recover an infective quantity of virus from the blood of human beings or of experimental animals suffering from paralytic poliomyelitis have been unsuccessful. Finally, should the virus of poliomyelitis actually pass through the placenta it might be that it would be attenuated or even neutralized by the activity of virucidal substances peculiar to this organ. McKhann and Chu (1933) prepared an extract from the placenta which contained only traces of female sex hormone, and stated that this preparation was capable of neutralizing the virus of poliomyelitis in vitro. Tezner and Goldhamer (1933) and Jungeblut, Meyer, and Engle (1934) called attention to the fact that poliomyelitis-virucidal substances could be demonstrated in placental extracts in certain cases where it was absent in the maternal serum. Whether this virucidal substance in the placenta is capable of inactivating the virus of poliomyelitis in vivo as well as in vitro is unknown.

### Conclusions

1. Some evidence was presented which may indicate that chorionic gonadotropin, or some substance associated with the formation or metabolism of this hormone, might play a role in increasing the resistance of the pregnant female during the first trimester of pregnancy to the virus of poliomyelitis.

2. There was no evidence that infective quantities of the Armstrong-Lansing strain of the virus of poliomyelitis were transmitted from the mother to the nervous tissues of the fetus in utero, or from the mother to the nervous tissues of her offspring through the secretions of the mammary glands.

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## CARCINOMA OF THE CERVIX, END RESULTS\*

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ONE of us, in 1931, made an evaluation of high voltage roentgen therapy in the treatment of carcinoma of the cervix. The study was based upon the duration of life of 437 women with cervical cancer, who had been treated in the radiologic department of the Philadelphia General Hospital, and followed until their deaths.<sup>1</sup> This unconventional approach was adopted because of the peculiar character of the material available in our clinic. Lesions less advanced than Stage III were encountered so infrequently that too few patients survived the five-year period to provide material for reliable statistical comparisons. Of the 437 cases included in the above report, there were only one in Stage I and three in Stage II (Schmidt's classification). Our primary purpose in the investigation was to determine whether high voltage x-ray therapy was of any value in the treatment of this disease. We were also interested in learning whether subsequent reports based on the five-year survival rate, would confirm the impressions obtained from our study.

The "five-year arrest" has for years been the standard by which the value of treatment for carcinoma of the cervix has been measured. Though undoubtedly the best basis for comparison of therapy so far provided, it has many limitations. Treatment with a high primary mortality rate, or subject to frequent undesirable complications, though it result in many "five-year cures," may be less desirable than another method involving a lower initial mortality and fewer complications, but with a smaller number of patients symptom-free five years after treatment. The objective in cancer therapy should be not only to arrest permanently a great percentage of cases, but also to render the incurables useful and comfortable for as long as possible. We believe, therefore, that the duration of life after admission is, per se, a proper feature to consider in appraising the results of any form of therapy. Subsequent reports by Scheffey<sup>2</sup> and others based on "five-year arrests" have confirmed the findings of our original study.

In our clinic previous to 1928, cancer of the cervix in Stages I, II, and III, was treated with radon in a cervical T tube, with filtration of 0.5 mm. silver, 1 mm. brass and 2 mm. rubber. The dosage was 2,400 mc. hrs. Tragic accidents such as perforation of the uterus, rapidly spreading peritonitis, and septicemia following the use of radon in Stage IV cases, caused us to discontinue radon therapy in such ad-

\*Read at a meeting of the Philadelphia Obstetrical Society, October 7, 1943.

vanced lesions, and most of these patients received no treatment at all. Some were given applications of high voltage roentgen therapy through two or four external ports. In the light of our present knowledge, the dosage of this external irradiation was invariably inadequate.

From 1928 to 1931, all patients whose general condition permitted, were treated with high voltage therapy, regardless of the extent of the disease. The usual dosage consisted of 1,600 to 1,800 r. (air) to each of four to six fields, 15 by 20 cm., depending upon the size of the patient. In the late stages, this was the only form of treatment given. Lesions in the first, second and third stages were treated with radon in the cervical and uterine canal, radon against the vaginal portion of the growth, and high voltage roentgen rays. The intracervico-uterine application was made with a filtration of 0.5 mm. silver, 1 mm. brass, and 2 mm. rubber. The capsules in tandem varied in number depending on the length of the uterine cavity. The dosage ranged between 2,000 and 3,000 mc. hrs., depending upon the depth of the cervical canal. The vaginal application of radon was made in three sittings. 1,000 mc. hrs. of radon with a filtration of  $\frac{1}{2}$  mm. silver, 3 mm. lead and rubber (approximately equivalent to 2 mm. of platinum) at a distance of 1 cm. were applied transversely against the cervical growth and into each vaginal fornix, to provide a three-directional cross-fire, totaling 3,000 mc. hrs. The high voltage x-ray therapy was administered with the four- to six-field technique developed by Weatherwax and Widmann<sup>3, 4</sup> of our clinic.

Soon after adopting the policy of treating Stage IV cases with high voltage x-ray therapy alone, but in adequate dosage, we sometimes observed rapid regression of both the primary tumor and the parametrial infiltration, so that the cervix recovered more or less of its mobility. Since 1931, many Stage IV patients responding favorably in this respect were subsequently treated with the standard dosage of radon into the uterine and cervical canals, and against the vaginal portion of the cervix, and six to eight weeks later a second course of high voltage radiation was given. Since 1938, an ever increasing number of our patients have also been treated with transvaginal high voltage x-ray therapy. In other respects our technique from 1931 to the present time has been identical to that employed from 1928 to 1931.

During this later period, 1931 to 1942, 579 additional patients, treated on the radiologic service of Philadelphia General Hospital, have died. It seems desirable at this time to compare the results secured in this second group with those obtained between 1922 and 1931, when different radiologic techniques were practiced, and to learn if possible the reliability of statistics based on the duration of life after admission.

Since 1931, five patients in Stage I have died. One of these patients, aged seventy-two, died thirteen days after admission from gangrene of the foot due to arteriosclerosis, without treatment for her carcinoma. A second patient, whose lesion was in the first stage at the time of treatment, is of passing interest because of surprising findings at

TABLE I. CASES ARRANGED IN STAGES (SCHMITZ)

CARCINOMA OF CERVIX	
END RESULTS	
STAGE	NO. OF CASES
I	5
II	27
III	168
IV	260
V	119
Total	579

autopsy. She lived only ten months after her treatment, and at the time of her death, metastases were found in the lungs, liver and peritoneal cavity, yet the primary lesion had been destroyed and there was no discoverable involvement of her parametrial tissues by the growth. Four treated patients lived an average of 9.5 months after treatment as compared with the single Stage I patient in our earlier group who survived for twenty-one months.

Of the 27 patients in Stage II, one refused any treatment and another, after having been treated with radon, refused high voltage x-ray therapy. The average life span after admission for the 20 patients in this stage, who were treated with high voltage x-ray therapy and radon, was 17.2 months. Five other patients whose treatment, for various reasons, was incomplete, averaged only 6.8 months of subsequent life. In our previous report, three patients in Stage II, who had died, lived an average of 13.3 months.

Fig. 1 is concerned with two groups of patients in Stage III. The cross-hatched columns representing patients admitted before 1931 and the solid columns, those admitted since then and numbering 166. Eleven of these patients received no treatment at all, and their average life duration was 4.6 months. Twelve cases, treated only with radium, lived 9 months after admission. Ninety-nine cases receiving external roentgen irradiation and radon, died an average of 18.8 months after treatment; whereas 46 patients who were treated only with high voltage x-rays, applied externally and in some cases transvaginally, lived an average of 10.8 months. By comparing the survival time of these women with those in our earlier group, it will be seen that the untreated cases which occurred in approximately the same proportion, lived just a little longer. Eight of these refused treatment and three died of other causes before treatment could be started. The twelve patients who were not given high voltage x-ray therapy, had refused this supplemental treatment. The average duration of their lives was slightly higher than in those of the first series. The ninety-nine patients receiving our standard treatment with high voltage x-ray therapy and radon, lived an average of 18.8 months, an improvement of seven months (40 per cent) over the group reported in 1931. Forty-six patients treated with only high voltage x-rays externally and transvaginally, lived an average of 10.8 months, an improvement of almost four months (50 per cent), when compared with the 1931 cases. It should be recalled that the present series received a higher dosage of external irradiation and some, in addition, transvaginal irradiation.

In Stage IV, there were 260 patients admitted since 1931. (Fig. 2.) Eighty-five of these received no treatment, either because they refused it, or because their physical condition precluded even the administration of external high voltage x-ray therapy. The average duration of life in the untreated cases was 1.8 months. Four patients had intravaginal applications of radon with 0.5 mm. silver and 5 mm. lead filtration at a distance of 1 cm. and lived an average of 8.66 months. In ten patients, following high voltage x-ray therapy, the tumor had regressed so that the cervix was again movable, and these were subsequently treated with radon. These lived an average of 13 months. One hundred and sixty-one cases, treated with external high voltage therapy alone, lived an average of 7.9 months. Fig. 2 shows that while the average duration of life in the Stage IV cases who received no treatment was practically the same as in the group reported previously, those treated with radon heavily filtered, and applied at a distance, lived more than twice as long as the Stage IV cases in the 1931 group

*Carcinoma of Cervix (stage III)*  
—End Results—

1922-1931 ~ ▨ ■ ~1931-1942

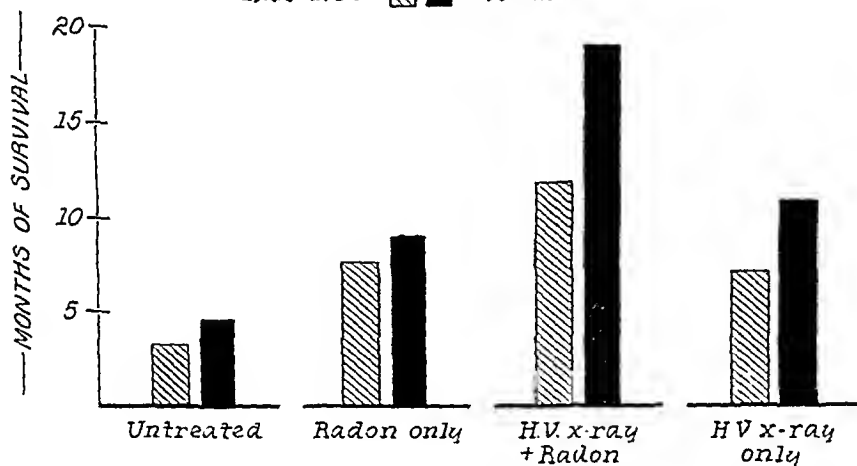


Fig. 1.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. Few patients were untreated in either series.

who were treated with lightly filtered radon applied intracervically. The patients of the present study in Stage IV treated with x-ray therapy and radon also lived twice as long as those previously reported. It is our opinion that this increased survival time was due to the fact that the radon was applied only in those cases where high voltage x-ray therapy was followed by localization of the primary tumor, and disappearance of the parametrial infiltration. The fixation of the pelvic organs in these instances may have been due to inflammatory exudate, rather than to extension of the neoplasms. Aware that in some clinics these patients would be reclassified into Stage III, we believe such practice to be confusing and retain the classification decided upon when the lesion was first seen by us. The 161 patients treated with high voltage x-ray therapy alone, were those in whom sufficient regression to make them suitable for later radon application failed to occur after high voltage x-ray therapy. It is therefore not surprising that in this series the patients treated with x-rays alone had a shorter survival time than those who subsequently received radon, or that



there was little difference in the life span after admission with x-rays alone in the two series.

One hundred and eighteen cases, about 20 per cent of the patients admitted since 1931, were classified as in Stage V. (Fig. 3.) All of these women were sent to our clinic from other hospitals in the Philadelphia area, and a large proportion of them were unsuitable for even external irradiation with high voltage therapy. There were 60 such cases who survived an average of 2.4 months. No Stage V lesions in our later group were treated with radon alone. Seven patients after being treated with high voltage x-ray therapy were regarded as suitable for subsequent radon irradiation. Their average survival time was 14.1 months. The remaining 52 patients were treated with high voltage x-ray therapy only. Their average life duration after admission was 12.4 months. In Fig. 3, it will be seen that the average duration of life of 2.4 months is approximately that observed in untreated Stage V cases in our earlier report. The average duration of life after admission in those treated with radon and high voltage therapy is only slightly more than that in the first series. That the patients treated with high voltage x-ray therapy only, survived almost twice as long as those previously reported may be due to the fact that more adequate dosages were applied.

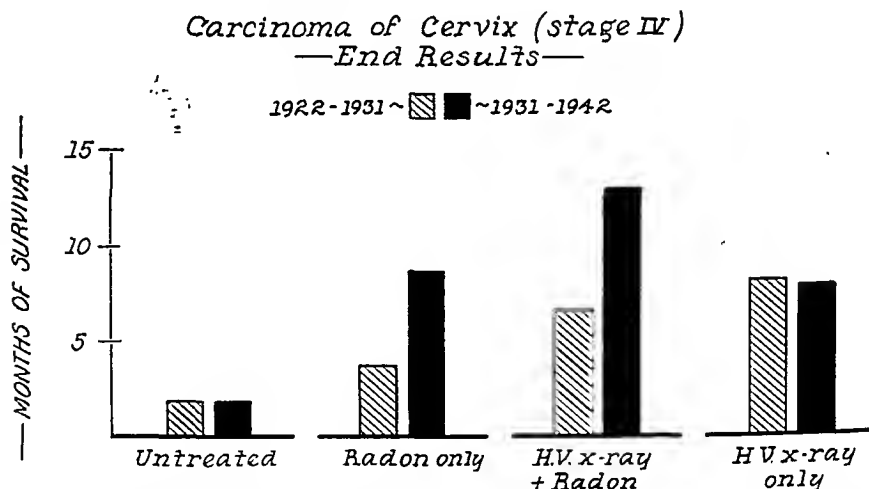


Fig. 2.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. Untreated patients survived equally long in both series.

The present report, based on the histories of 580 patients suffering from carcinoma of the cervix, again demonstrates the value of high voltage roentgen therapy in the treatment of this disease. The importance of the later observations is enhanced by comparing these results with those of the earlier report concerning 437 patients; a grand total of 1,007 women suffering from cancer of the cervix, who died on the radiologic service of the Philadelphia General Hospital since 1922. Stage IV lesions, treated with external irradiation of high voltage x-ray therapy alone, lived longer than those treated with lightly filtered radium alone. The best results, however, were secured in the group who, after regression of the primary lesion had been brought

about by preliminary high voltage x-ray therapy, were subsequently treated with heavily filtered radon at a distance of 1 cm. Since this fact became apparent, it has become our policy to administer external high voltage x-ray therapy preliminary to the radon application in every case of carcinoma of the cervix. The longer duration of life in patients in the recent series who were treated with high voltage x-ray therapy, regardless of the stage of the disease, we believe can be attributed to the fact that these were given more adequate dosage than those of the 1931 study. Our findings in relation to the patients of both series who received no treatment at all, approximate each other so closely that we feel justified in recommending this method of study when it is desirable to evaluate the results of treatment of carcinoma of the cervix without waiting for a large number of patients to have passed the five-year period.

### *Carcinoma of Cervix (stage V)* —End Results—

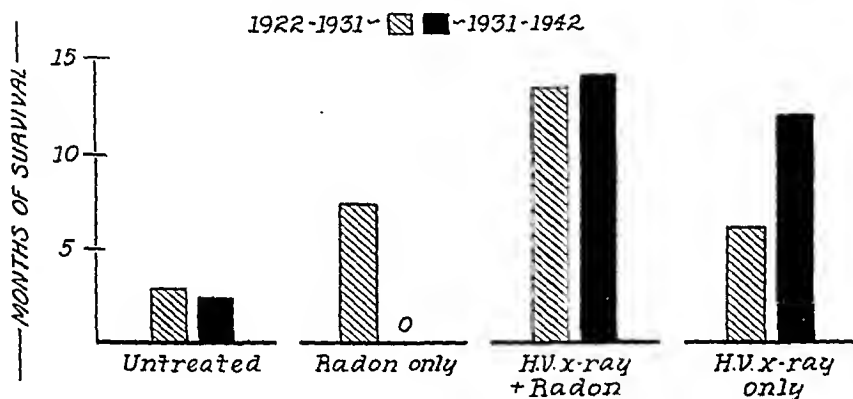


Fig. 3.—Comparison of the duration of life after different forms of treatment. In the earlier series the radon and x-ray dosages were smaller and the filtration was less. None in the later series were treated with radon alone.

### Summary

1. When the general condition of the patient permits, every case of carcinoma of the cervix should be treated with some form of irradiation therapy.
2. External high voltage roentgen therapy is always beneficial and safe for even the most advanced stages of the disease.
3. In many apparently advanced lesions, preliminary x-ray therapy will result in sufficient regression of the lesion that radon may be applied subsequently to great advantage.
4. Heavily filtered radon applied at a distance of one centimeter, results in better palliation than the highly filtered radon in contact application.
5. By observing the duration of life after admission to service in patients who died from carcinoma of the cervix, a satisfactory indication of the value of various forms of therapy may be obtained.

## Factors Employed in High Voltage Roentgen Therapy

Two hundred kv., 20 ma., 50 cm. F.S.D., 0.5 mm. Cu. plus 1.0 mm. A.C. filter, half-value layer 0.95 mm. Cu., 15 by 20 cm. fields, 4 to 6 ports, all fields directed to the cervix. Dose 2,000 r. (air) approximately 3,000 r. (tissue) delivered to the tumor. Patients treated on alternate days giving 150 r. to each of 4 fields until tumor receives 3,000 r. (tissue). Approximately three weeks.

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## Discussion

DR. LEWIS C. SCHEFFEY.—With a large number of patients having advanced cervical lesions (Groups III, IV, and V), Dr. Behney and Dr. Howson have clearly shown how the duration of life can be prolonged by adequate irradiation treatment. I would be interested also to have Dr. Behney tell us approximately what his five-year survival rate has been in these patients with such advanced disease.

Our experience in the uterine carcinoma clinic of the department of gynecology at Jefferson Medical College Hospital has been similar. Our most recent report, published in *Radiology* in May, 1943, covers a sixteen-year survey of nearly 300 patients treated between 1921 and 1937. Of these, less than 40 per cent were treated with both radium and x-ray, for it was only since 1931 that x-ray began to be used at all frequently in conjunction with radium. Not until 1934 to 1935 was x-ray employed as a routine procedure prior to the application of radium. Even so, the five-year survival rate for patients treated in the latter fashion is substantially better when compared to those patients treated differently: i.e., 30 per cent (relative cure rate), as opposed to 13.9 per cent when the x-ray was used subsequently, and 16.6 per cent when it was used both before and after radium. It will be of vital interest to us to note whether or not the continued use of the present method will maintain this improved survival rate when our next five-year report is presented in 1946 to 1947, especially since transvaginal therapy has been employed as an added port during the past two years.

DR. BERNARD P. WIDMANN.—As a radiologist I can allude to some of the technical procedures which we carried out and which, I believe, contributed something to improving the end results. Since 1931, we have carried out a statistically and predetermined plan of treatment so that if a patient completed a series of treatment we knew how much she had had. Prior to that, we had had a manifold experience with varied techniques.

It is impossible to give more than the equivalent of about 2,000 r. or sometimes 3,000 r. tissue dosage. If you give more than that in about three to four weeks, you reach a treatment dose beyond the capacity of the individual. In the advanced group of cases we think it is better to give a series of x-ray treatments before radium is given. The interval between the two is about six weeks.

When the radium is finally given in a Stage III or IV case, we feel that it is a mistake to give a treatment with a single capsule, which would cover a length of 20 to 24 millimeters. If it is possible to get into the uterine canal and extend the treatment to 9 centimeters we irradiate a larger area. When you give 2,000 or 3,000 milligram hours you are giving a very large dose—as much as 30 to 45 erythema doses. It must be remembered that ninety per cent of the irradiation is absorbed in the first

centimeter of tissue. If you give a larger dose, 3,000 to 4,000 milligram hours, the irradiation extends beyond that.

There are some cases where you can supplement with a vaginal radium tampon against the cervix. If you use a filtration of 2 millimeters of platinum at 1 centimeter distance, you can give as much as 3,000 milligram hours but it will give a reaction so that two to three years later you have a marked stenosis of the posterior half of the vaginal vault. Because of that possibility, we think it is better to divide the treatment in one-third or one-half, and possibly you will be able ultimately to give as much as 4,000 milligram hours.

We are also trying out the so-called intra-cavitary treatment with cone and x-ray. We use it only in advanced cases, but when you get a frozen pelvis, you cannot twist the cone around in the pelvis. I do not know whether vaginal treatment with the high voltage x-ray is going to be equal to the radium.

With the higher voltage and a thicker filter you get a better depth dose but the quality of radiation does not have a better effect on the carcinomatous tissue than the 200,000 volt. The wave length which the dermatologist uses is also just as effective, but there is the difference in getting the depth dose. If the patient is measured accurately, you can add more fields of treatment and deliver just as effectual irradiation if you use the new supervoltage machine. The point is, to deliver an equivalent of about 3,000 tissue r., repeat about six to eight weeks later, and then supplement it with radium. I think you can then consider you have given the patient the benefit of everything which x-ray and irradiation can offer.

DR. OWEN J. TOLAND.—I was interested to see the short survival rate in the grade four and five carcinomas. This raises a point of extreme importance which was not mentioned. If with this combination of radiation methods the survival rate is as low as fifteen months, I would like to raise the question of whether Dr. Behney thinks those patients are more comfortable with treatment. If not, we had better drop radiation therapy and treat with acetone and morphine.

DR. BEHNEY (closing).—When the original paper (1931) concerning this unconventional method of evaluating treatment for carcinoma of the cervix was written, the benefits of high voltage x-ray therapy were, to say the least, viewed with suspicion by the majority of gynecologists. While we, at Philadelphia General Hospital, were convinced of its value, and had treated many patients with this agent, there were too few who survived five years after treatment to furnish satisfactory statistics. The object of the study was to determine whether high voltage therapy was of any value in the treatment of this disease. This, I believed, would be apparent if patients so treated lived longer than a control series of patients, with a similar degree of involvement, who had not received x-ray therapy. Subsequently, as mentioned, reports based on five-year survivals of patients treated with high voltage therapy were in accord with the impressions gained from the original study.

The present presentation, a continuation of the original study, includes approximately five hundred additional cases, still provides a number far short of that considered desirable by statisticians. We hope that other gynecologists will review their records in a similar manner. If this method of evaluation were proved acceptable, it would enable one to appraise the value of treatment for cancer without waiting from five to ten years to collect a large number of five-year survivals.

In addition to those considered in this report, we have a number of patients who have lived beyond the five-year period. Many of them are still living, some twenty years after treatment. Since this method of evaluation is based on the duration of life after treatment, living patients cannot be included here. In reply to Doctor Toland, I should like to say that in our opinion patients treated with high voltage therapy have definitely less pain than those who do not receive it. This point has been stressed in other reports by us, as well as by many other observers.

## SALMONELLA INFECTION IN GYNECOLOGY\*

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HUMAN infection with the *Salmonella* bacilli have been reported much more frequently in recent years. It was believed that the characteristic syndrome produced by this organism was gastroenteritis or "food poisoning." However, as a result of improvement in bacteriologic technique, it is evident that infection by these organisms is much more frequent and may produce a variety of clinical syndromes. More than one hundred types of *Salmonella* organisms are now recognized by cultural and serologic methods. They are divided into six main groups.

The most common organism resulting in clinical infection is *Salmonella typhi* murium. It was found 369 times among 1,000 human *Salmonella* infections at Beth Israel Hospital in New York City.<sup>1</sup> Septic infections, enteric fever and gastroenteritis are the most common types of infection encountered. Although it is still generally believed that these infections are due to the ingestion of contaminated food, it is possible that they may be transmitted "through the handling of animal carcasses, bathing in polluted waters and by transfer from man to man either directly, by insect vectors or by contact infection from food, dishes or nursing bottles."<sup>2</sup>

Pelvic infection caused by the *Salmonella* bacilli have been recognized with extreme rarity. Two cases of postabortal sepsis<sup>3, 4</sup> and single cases of post-partum sepsis,<sup>5, 6†</sup> infected fibromyoma uteri<sup>7</sup> and infected hematocoele<sup>8</sup> have been reported in addition to three cases of infection of the tubes and ovaries.<sup>9-11</sup> (Table I.) To these we would like to add two additional cases of salpingo-oophoritis caused by a *Salmonella* bacillus.

### CASE REPORTS

CASE 1.—A. W., a 33-year-old nullipara, was admitted to the Beth Israel Hospital complaining of right lower quadrant pain. One year ago, she experienced severe right lower abdominal quadrant pain and fainting for which she was hospitalized elsewhere. Since that time, she has had repeated attacks of abdominal pain and fever, attributed to "inflamed tubes." In the past six months, she had noticed a purulent discharge from the rectum. She had been married six years and had never been pregnant. Menses began at 14, occurred regularly every 28 days and lasted 3 days. The last menstrual period occurred 18 days before admission. The past history was irrelevant.

\*This is part of a study of the bacteriology of tubal infection undertaken by a grant from the Greater New York Fund.

†(6) Refers to Roth's case.

TABLE I

AUTHOR	DIAGNOSIS	ORGANISM	SOURCE OF INFECTION	AGGLUTINATION TEST	REMARKS
Bornstein Saphra Strauss	Septic abortion	<i>S. Cholerae Suis</i>	Not stated		Positive blood culture
Ten Broeck Li Yu	Septic abortion	<i>S. Paratyphoid C</i> (?)	Not stated	Positive	Positive blood culture
Roth	Puerperal	<i>S. Suipestifer</i>	Not stated		Suipestifer obtained from empyoma subsequent to puerperal sepsis
Gray	Infected myomas	<i>S. Suipestifer</i>	Not traced	Weakly positive	Prolonged febrile illness with positive blood culture
Brown	Bilateral pyosalpinx	<i>S. Newport</i>	Not traced	Positive	Illness of one month preop.; discharged 30 days postop. Blood culture sterile
Herring Nicholson	Acute bilateral salpingitis	<i>S. Cholerae Suis</i>	Handling of infected pigs ?	Positive	Prolonged postop. course. No blood culture
Jager Lamb Brown	Right salpingitis and pelvic peritonitis	<i>S. Suipestifer</i>	Not traced	Positive	Ill 4 days, diagnosis of acute appendicitis
Biddle	Infected hematocele	<i>S. Suipestifer</i>	Not traced	Positive	Positive blood culture

On physical examination, she appeared to be chronically ill and moderately anemic. There was tenderness in the right lower abdominal quadrant and a sensation of an ill-defined mass.

On vaginal examination, the external genitalia were normal; cervix conical, the fundus of the uterus was anteflexed, normal in size and to the patient's left. The cul-de-sac was filled with a hard, globular mass continuous with that felt abdominally. This mass was somewhat irregular and not particularly tender.

Temperature 99.6° F., pulse 90, respiration 24, blood pressure 120/70, Urine showed a faint trace of albumin; rare red and white blood corpuscles, hemoglobin 98 per cent; red blood corpuscles 4,600,000; white blood corpuscles 6,500; polys 80 per cent; sedimentation rate 30 mm. in 45 minutes.

Following vaginal examination on the third day of admission, temperature rose to 102.4° F. and for four weeks varied between normal and 102° F. At this time, two distinct masses were palpable on vaginal examination, the one to the right being somewhat globular and cystic, whereas the one to the left was sausage-shaped.

The sedimentation rate varied from 15 mm. to 40 mm. in 45 minutes. The hemoglobin dropped to 70 per cent and red blood corpuscles to 3,500,000. The white blood corpuscle and differential count remained within normal limits. Smears and cultures of the cervix and urethra were negative for gonococci. Blood cultures were negative.

Since no improvement had been evident following one month of palliative therapy and the mass seemed to be pointing in the cul-de-sac, a posterior colpotomy was performed. No pus was obtained. For ten days following colpotomy the temperature curve seemed to be lower, but then daily rises in temperature, 101° F. to 102° F. recurred.

For the following five weeks she was treated with a variety of agents. Bed rest in Fowler's position, high calorie diet, forced fluids, insulin and transfusions were given. Sulfadiazine was attempted but had to be discontinued because of marked anemia. Injections of aolan produced a transient lowering of the fever. Vaginal diathermy was administered. Although her temperature gradually receded, she again complained of lower abdominal pain and the sedimentation rate remained persistently elevated, varying from 20 to 50 mm. in 45 minutes.

As there seemed to be no improvement in her condition, a laparotomy was performed eleven weeks after admission and seven weeks after the colpotomy. At this time the sedimentation rate was 38 mm. in 45 minutes. The blood count was normal except for a moderate anemia. The temperature level was about 100° F. At operation the right ovary was the site of an abscess about 12 cm. in diameter. The right tube was stretched over this abscess and was elongated, thickened and chronically inflamed. The left tube was thickened and adherent to the posterior wall of the uterus. A loop of ileum and the sigmoid were densely adherent to the abscess. The adhesions were dissected free from the mass and the right tube was cut away from the uterus, thereby exposing the ovary which was separated by blunt and sharp dissection from the surrounding structures. When the mass was almost completely mobilized it ruptured and a large quantity of foul-smelling pus escaped. Culture taken. A supra-cervical hysterectomy and bilateral salpingo-oophorectomy was performed. The posterior lip of the cervix was then split through its entirety and the cervical cuff removed from the vagina. A Mikulicz drain was inserted into the

vagina and peritonealization secured. Ten grams of sulfanilamide powder were left within the abdominal cavity.

*Pathological Report.*—(Dr. Plaut). Hyperemic, rather small body of uterus, 5 cm. high, tubal angles 5 cm. apart, anteroposterior diameter about 3 cm. Left tube and ovary are attached. They are bound together by adhesions and form a soft, irregularly ovoid mass, 4.5 by 3 by 2 cm. The uterine cavity is normal in width, the endometrium is thin, moderately hyperemic. There are several small myomas. The abdominal ostium is closed, the remnants of the fimbriae are attached to a star-shaped scar. The ovary which is adherent is edematous. Large adnexal mass consisting of a flat ovoid portion, 8 by 7 by 3 cm. and one having the shape of tube which is 11 cm. long. The large ovoid mass, after fixation, consists of a thick-walled cyst with thick yellowish festooned lining. On cross sections of the tube, the lumen cannot be distinguished. The cut surfaces appear spongy, partly homogeneous and grayish.

*Microscopic.*—Characteristic picture of severe chronic salpingitis with growing together of inflamed folds. Large areas in the outer layers are occupied by leucocytic inflammation. In the one tubal angle, the folds are moderately thickened and the number of nuclei in them is increased. Most of these nuclei, however, are spindle-shaped. The outer layers are more cellular than normal, with some round nuclei. The other tubal angle is practically normal. There are old tuboovarian adhesions and there is some chronic inflammation in the ovary. The endometrium is rather thin, partly bloody. It corresponds to an early proliferative phase. The cervix is not unusual.

*Diagnosis.*—Chronic salpingo-oophoritis. Small myomata uteri. The postoperative course was uneventful except for infection of the wound which was noted at the upper and lower angles on the ninth postoperative day. A considerable amount of pus was evacuated. The patient was discharged on the thirtieth postoperative day with a normal temperature. The abdominal wound was clean. The abdomen was soft with no tenderness or pain present. On vaginal examination, the stump of the cervix was felt to be high in the cul-de-sac and surrounded by an area of induration which was not tender or painful.

#### Bacteriology:

Dr. E. Seligman.—Smear of the pus recovered at operation showed gram-positive cocci, gram-positive rods, gram-negative rods, gram-negative extracellular diplococci, and polymorphonuclear leucocytes.

*Salmonella typhi murium* was grown from the pus in the tuboovarian abscess. A positive culture of this organism was also obtained immediately postoperatively from the patient's stool and on the ninth postoperative day from the pus of the wound infection. The stool was still positive for *Salmonella* at the time of discharge, but became negative three months later. Agglutination test for *typhi murium* was positive in a dilution 1:320.

She was seen one month later at which time she was completely free from symptoms; she had gained weight; the wound was well healed; the stump of the cervix was high up and the induration surrounding the cervix, noted at the time of discharge, was much lessened in amount.

CASE 2.—M. W., a 28-year-old divorcee, was admitted to Beth Israel Hospital with the chief complaint of bilateral lower abdominal pain prior to and during menstruation for the past three years. She had been divorced 5 years ago. Three years ago she had had an attack of acute



lower abdominal pain with fever and since then she had had occasional attacks of pain, fever and severe dysmenorrhea. She was gravida v, para iv, last pregnancy five years ago. Menses began at 12, were regular every 28 days and lasted 4 to 5 days. There was no increase in the amount of vaginal bleeding. The last menstrual period was ten days before admission. Appendectomy had been performed thirteen years ago. Temperature 99° F., pulse 80, respiration 24, blood pressure 115/80. Physical examination was normal except for the pelvic findings. There was a well-healed right rectus scar. There was no abdominal pain, tenderness or mass present. Multiparous vaginal introitus. The cervix was enlarged and bilaterally lacerated. Motion of the cervix produced some pain in the left lower abdominal quadrant. The uterus was normal in size, anterior in position and somewhat fixed. There was tenderness in both fornices with some thickening of the left tube.

The urine, blood count and sedimentation rate were within normal limits. Blood cultures were not done.

A diagnosis of chronic salpingitis was made and the patient was operated upon three days after admission. At operation both tubes were inflamed and thickened and there were numerous filmy adhesions between the tubes and ovaries. A right parovarian cyst, 1 cm. in diameter, was present. The uterus was normal in size, shape, and position. Both ovaries appeared normal. A bilateral cornual resection was performed.<sup>12</sup> The right parovarian cyst was punctured.

*Pathologic Report.*—(Dr. Plaut.)

*Microscopic:*

*Right Cornu.*—Adenomyosis of tubal angle. The glandular structures themselves are not inflamed. In the adjoining muscle tissue slight perivascular accumulations of round cells are noted.

*Left Cornu.*—Midportion of tube in cross section and oblique section. The folds in places are somewhat thick but there is no inflammation.

*Diagnosis.*—Adenomyosis of tubal angle.

Culture (Dr. Seligmann) of the cornual portions of the tubes was reported as being positive for *Salmonella typhi murium* in pure growth. Subsequent cultures of the feces were reported as being negative for this organism. Agglutination tests done immediately upon report of the culture were negative in a dilution of 1:40. One week later the agglutination test was positive in a dilution of 1:80.

## Discussion

The method by which these organisms infect the tubes and ovaries is of some interest but cannot be stated with certainty at this time.

1. Infection via the blood stream is believed to be the usual route whereby localized septic metastasis such as osteomyelitis, empyema, etc., is usually produced. In such septic infections a positive blood culture may be frequently obtained. *Salmonella* organisms have been cultured from the blood in postabortal and puerperal sepsis, in infected myomas and in infected hematocele. Unfortunately there is no instance of positive blood cultures reported in any case of *Salmonella* salpingo-oophoritis, although by analogy it would seem that the infection is probably hematogenous.

2. Ascending infection from the vagina and uterus. In the three cases of *Salmonella* infection of the tubes reported in the literature, it

is of interest that none showed *Salmonella* infection in the culture of the feces. Of the two cases herein reported, in one the stool was positive for *Salmonella typhi murium*, which is the first time that this finding has been observed. It is believed that the rectal pus was secondary to minute or incomplete perforation of the ovarian abscess into the rectum.

3. Infection of the tubes and ovaries by direct extension from the intestines. Such infection to a normal tube and ovary from the intestine seems improbable. However, it is well known that secondary invasion by intestinal organisms to a pyosalpinx or tubo-ovarian abscess in adherent tubes and ovaries may occur.

4. Other sources of vaginal infection (prostatic secretion, salivary contamination, etc.) have not yet been demonstrated although such a possibility cannot be denied at the present time.

In Case 1, the presence of extracellular gram-negative diplococci in the smear of the ovarian pus recovered at operation, suggests the possibility of a preceding gonorrheal salpingo-oophoritis. In Case 2, the occurrence of pelvic infection subsequent to divorce is clinically suggestive of gonorrheal salpingitis, but there are no laboratory findings to confirm this possibility. However, it seems likely, but unproved, that in both cases the tubes had been the seat of a previous infection, and constituted a locus minoris resistentiae to subsequent infection with the *Salmonella* organism. Whatever the method of inoculation, the positive agglutination tests in both cases herein reported as well as in the three cases previously reported, definitely indicate that this organism is not a contaminant.

It would appear that in many infections of the tube and ovary in which gram-negative bacilli are found and which heretofore have been considered to be coli infections may prove to be of *Salmonella* origin.

Until our second case was found to be of *Salmonella* infection on routine bacteriologic study, it was believed that the clinical course of *Salmonella* salpingitis was characterized by a prolonged febrile illness which did not respond to the usual therapy instituted for pelvic infection. It has been repeatedly observed that in a patient with pyosalpinx, the temperature will drop to normal within three weeks following the institution of bed-care and supportive treatment. Ovarian abscesses may not respond as quickly, but also tend to subside although the period of time is more prolonged. However, in Case 2 there is no evidence of protracted illness, in fact, the infection was obviously inactive on admission. Notwithstanding, it would seem that the possibility of *Salmonella* infection should be considered in patients with pelvic infection who are refractory to the ordinary methods of therapy.

The treatment of *Salmonella* infection of the tube would not seem to differ from that of tubal infections caused by other organisms. This has been described in detail elsewhere.<sup>13</sup> Although no generalization

can be drawn from so few cases, whether the treatment is radical, as in Case 1, or extremely conservative, as in Case 2, the end results have been satisfactory.

### Summary

1. Two cases of *Salmonella* infection of the tubes and/or ovaries are reported. Three additional cases were found in the literature.

2. In one of the two cases presented, a positive stool culture of *Salmonella* is reported for the first time.

3. The route of infection has not been definitely ascertained, although blood stream infection (possibly to previously infected tubes) is not unlikely.

4. The positive agglutination tests indicate that the *Salmonella* bacilli are of etiologic significance in the causation of pelvic infection and are not accidental contaminants.

5. The manifestations of such infections are not clinically distinctive. Certain identification can be made only by bacteriologic and immunologic methods.

6. The treatment would not seem to differ from that of salpingitis caused by other bacterial organisms such as the gonococci.

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# THE UTERINE MOTILITY ASSOCIATED WITH POSTERIOR POSITIONS OF THE OCCIPUT

## Observations Made With the Lóránd Tocograph

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THE reason why the occiput presents in the posterior position is not known. And why, when such presentations occur, engagement fails to take place, or, after it has occurred the occiput fails to rotate anteriorly, are sometimes questions which are difficult to answer, especially while labor is in progress.

Lack of satisfactory answers to these questions raised the additional question as to whether greater knowledge of the uterine contractions might aid in the solution of some of them.

With these thoughts in mind, we re-examined our tracings of uterine motility, secured with the assistance of a Lóránd tocograph,<sup>1, 2</sup> either before or during the labors, of patients whose infants happened to present with their occiputs in the posterior position.

## Results

Women delivered in the hospital of the University of Pennsylvania between Jan. 1, 1938, and Dec. 31, 1942, acted as subjects. Table I summarizes the number of observations.

### Uterine Motility During Pregnancy

*Relation of Uterine Motility to Position of Occiput on Engagement.*—The uterine activity of 26 of the 55 patients (Table I) was registered before the onset of labor. The variety of the contraction patterns secured at this time was not unusual. It is concluded, therefore, that the character of the uterine activity, present prior to the onset of labor in all probability, had nothing to do with the position in which the occiput happened to present.

TABLE I. PATIENTS EXPERIENCING POSTERIOR PRESENTATIONS OF THE OCCIPUT

	PATIENTS
Occiput posterior presentations	55
Failure of the head to engage followed by cesarean section	5
Outlet dystocia followed by cesarean section	2
Delivered occiput anterior	20
Delivered occiput posterior	28
Tracings before delivery	26
Tracings during labor	28

### Uterine Motility During Labor

*Failure of Head to Engage.*—Five of the 55 patients (Table I) failed to engage the heads of their infants and were delivered by the ab-

dominal route. The pelves of these women were normal in size and configuration. The smallest of the 5 infants weighed 3,720 grams, the average for the group being 4,117 grams. Four of the 5 mothers were traced during labor and all registered a satisfactory uterine motility. These observations suggest that the size of the infant was the important factor in the failure of engagement.

The heads of 2 infants engaged but outlet contractions prevented vaginal deliveries; both women experienced normal uterine motility.

*Direction of Rotation of the Occiput.*—Twenty-three patients supplied tracings made during labor and were delivered vaginally. Their pelves were normal in size. Their infants varied in weight from 1,330 to 4,720 grams with an average of 3,377.

The relation between the quality of the uterine motility of these 23 patients, as revealed by the tocograph, and the direction of rotation of the fetal occiput are indicated in Table II. Of 11 patients who registered a satisfactory motility, 4 rotated the occiput to the anterior position, and of 12 who experienced poor motility, 4 also did so. This observation suggests that the successful rotation of the occiput to the anterior position did not depend upon the quality of the uterine contractions.

TABLE II. INFLUENCE OF QUALITY OF UTERINE MOTILITY UPON ROTATION OF OCCIPUT ENGAGING IN THE POSTERIOR POSITION

MOTILITY	PATIENTS		
	NUMBER	ROTATION	
		ANTERIOR	POSTERIOR
Good	11	4	7
Poor	12	4	8

The 11 infants whose occiputs rotated anteriorly weighed 3,476 grams on the average, and the 12 infants whose occiputs rotated posteriorly weighed 3,380 grams. The closeness of these two averages suggests that infant size did not influence the direction of rotation of the occiput, especially in view of the fact that the large infants rotated in both directions.

Since the quality of the uterine motility and the size of the infant did not appear to influence the direction of the rotation of the occiput, it would seem reasonable to infer that the direction of rotation was influenced chiefly by some other factor. The majority of the patients were not x-rayed, so for that reason we have no information which might throw light upon the influence of pelvic shape upon the direction of rotation of the occiput.

*Contraction Pattern.*—The patients exhibited a variety of contraction patterns during labor, but no one type of pattern predominated.

The patterns permitted themselves of classification in three categories: (a) normal motility, (b) primary inertia and (c) disproportion, examples of which are described below.

*Normal Motility.*—Normal motility is illustrated by the tracings reproduced in Fig. 1.

The patient, M. J., had had one previous pregnancy. Her pelvis was of normal size. The labor lasted 23 hours, and her contraction pattern was normal when registered on several occasions. The second stage of labor lasted only 1½ hours, yet the infant weighed 3,760 grams. The occiput delivered in the posterior position. Tracing (a), Fig. 1,

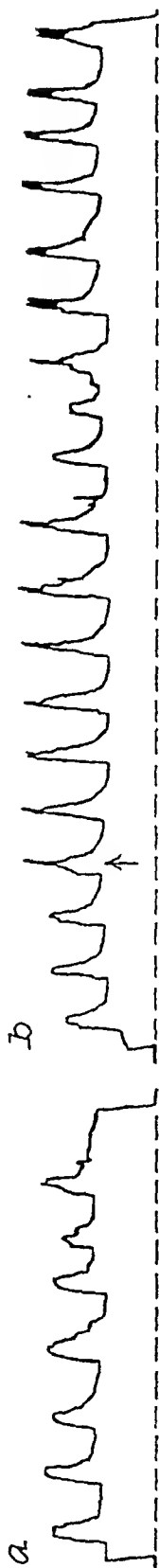


FIG. 1.—Patient M. F. Tracing (a) was recorded when the cervix was dilated 2 cm. Both the tonus and the contractions are normal. Tracing (b) was made late in the second stage of labor. The tonus and contractions are normal. Voluntary contractions of abdominal muscles start at arrow, and are indicated by "steeples" at crests of waves produced by the involuntary contractions. Both tracings are typical of normal motility during labor.



FIG. 2.—Patient V. C. Tracing recorded as cervix was beginning to dilate. The tonus is normal, but the contractions are weak. This tracing is typical of "normotonic" inertia.

was secured when the cervix was dilated 2 cm., and tracing (b) when the patient was ready for delivery. The wave at the arrow presents a "church steeple" at its crest. This results from the contractions of the abdominal muscles at the height of the involuntary uterine contractions. Both tracings reveal an average uterine tonus and contractions of average character and magnitude.

*Primary Inertia.*—This condition is illustrated in Fig. 2. The patient, V. C., was a primipara with a normal pelvis. Her labor lasted 53 hours, with a second stage of  $5\frac{3}{4}$  hours. Clinically her contractions were of poor quality throughout labor. The tracing shown in Fig. 2 was made just as the cervix was beginning to dilate, which was 41 hours after the onset of painful contractions, and only 12 hours before delivery. The infant weighed only 2,880 grams. The tracing shows that the patient was experiencing a normal tonus but her contraction waves were of unusually small magnitude. Inertia is indicated by the small size of the waves; and the presence of a normal tonus makes it possible to classify the inertia as being of the "normotonic" variety.<sup>3</sup>

*Disproportion.*—During a labor not complicated by the development of a disproportion, the uterus may or may not experience any progressive increase in tonus, but if it does, the increase usually is moderate in degree, even during the late second stage.

In the presence of normal contractions, disproportion affects the uterine motility by increasing the tonus of the uterus, which change is recorded readily by the tocograph. An example is reproduced in Fig. 3. The patient, E. R., was a primipara with a normal pelvis. Her labor lasted only 14 hours, but the second stage consumed 5 hours of it. She was delivered of a 4,150 gram infant at the outlet by forceps. Tracing (a), Fig. 3, was made when the cervix was dilated 2 cm. and before evidence of disproportion had developed. This tracing reveals a normal tonus and contraction waves of normal character and magnitude. Tracing (b) was made late in the second stage of labor and reveals evidence of disproportion. This tracing shows contractions of normal magnitude but an unusually high tonus, which is measured in terms of the distance of the wave troughs above the base line seen at the ends of the tracing.

### Comment

The number of patients forming the basis for this study is small, but it was unselected except for the fact that each patient happened to have her uterine motility recorded either before or during labor.

No tocographic observations are available to indicate the relative frequency with which unsatisfactory uterine motility accompanies labors not complicated by posterior positions of the occiput. Therefore, it cannot be stated with certainty whether the present patients experienced labors which were of unusually poor quality. The impressions have been gained, however, that the incidence of poor motility in these patients was not greater than the average, and that their contraction patterns in general were not of unusual character. In other words, it appears that posterior positions of the occiput are not necessarily accompanied by unsatisfactory uterine motility.

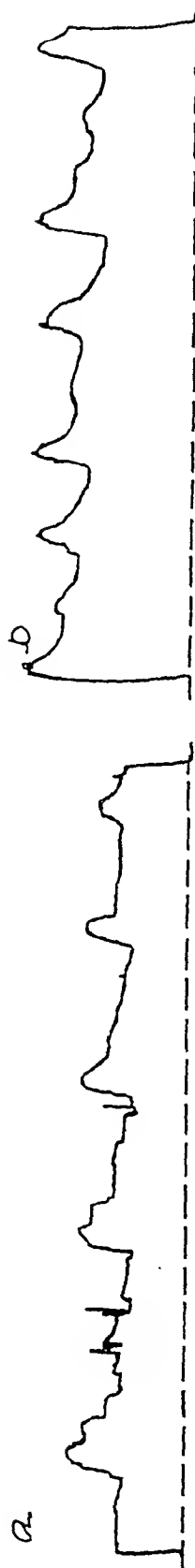


Fig. 3.—Patient E. R. Tracing (a) was made when the cervix was dilated 3 cm. The tonus and contractions are normal. Tracing (b) was registered late in second stage of labor. The contractions are normal, but the tonus greatly increased. An unusual increase in tonus is evidence of disproportion.



This study emphasizes several facts. The anterior rotation of a posterior occiput does not depend upon the quality, i.e., strength of the uterine contractions, or upon the size of the infant. If this is true the configuration of the pelvis in all probability plays the important role in directing the rotation of the occiput.

A second observation concerns the effect of disproportion upon uterine tonus when uterine motility is normal. The finding of a marked increase in tonus during labor should suggest to the obstetrician that he is dealing with a definite disproportion and, therefore, that he should be guided in his conduct of the patient's labor by this finding.

### Summary and Conclusions

1. Posterior positions of the occiput may be associated with either a good or a poor motility, and there appears to be no unusual tendency for the latter to occur.

2. The character of the motility before the onset of labor does not appear to determine the position of the occiput on engagement.

3. Disproportion is a more important cause of failure of engagement of a posterior occiput than is poor motility.

4. Poor motility is not the important factor in determining the direction of rotation of an occiput which engages in the posterior position.

5. In the presence of normal uterine contractions, disproportion results in an abnormal increase in uterine tonus.

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## THE VOORHEES BAG\*

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IN AN effort to evaluate the merits of the Voorhees bag we have reviewed our records for the 5½-year-period from January 1, 1938, to July 1, 1943. In this time there were 17,701 deliveries at the Elizabeth Steel Magee Hospital. The Voorhees bag was used 41 times for the following indications and with the enumerated results:

CASES	INDICATIONS FOR USE	FETAL DEATHS	MATERNAL MORBIDITY
9	Induction of labor	7	1
2	Placenta previa	2	1
3	Placenta ablatio	3	0
6	Fetal distress, due to cord complications	2	1
19	Inertial labor	5	6 1 Maternal death
2	Abnormal presentations	1	0

The 20 fetal deaths on analysis show that 2 infants were nonviable, weighing 970 and 1,300 grams; 1 was an anencephalic; 2 were hydrocephalics; on one other infant craniotomy was performed; 4 infants were premature, weighing less than 2,500 grams. In all instances the pregnancies were complicated by placental abnormalities or toxemias; 2 infants definitely and 3 probably had intracranial hemorrhages resulting from difficult deliveries. In 2 cases the cords were prolapsed on admission and in a third the cord prolapsed after a small bag used for induction was expelled; 1 infant died during labor and was macerated at birth; 1 infant probably died as the result of a severe nephritic toxemia in the mother.

Whether the Voorhees bag has a place in modern obstetrics is questioned by many. In recent years its use has undoubtedly decreased and in some centers has been eliminated. We are of the opinion that it still has its place in the obstetric armamentarium but only under certain conditions and for certain specific purposes.

The classic primary indications for the Voorhees bag as stated in the textbooks are: (1) to prevent bleeding, (2) to induce labor, and (3) to dilate or complete the dilatation of the cervix.

We feel that in marginal placenta previa, or in partial placenta previa in multiparas in which delivery by the vaginal route can be carried out, simple rupture of the membranes is easier, safer, and more efficient than introducing a bag. The cervix and lower uterine segment

\*Read at a meeting of the Pittsburgh Obstetrical and Gynecological Society, October 11, 1943.

in these cases is too friable to warrant any undue manipulation which might cause deep lacerations and hemorrhage. In the two cases in which a bag was introduced for placenta previa, the fetal mortality was 100 per cent, although heart sounds had been present. In one of these two cases a craniotomy was necessary to avoid lacerating the cervix, as too small a bag was introduced and dilatation was inadequate for delivery. The other infant was slightly premature, weighing 2,450 grams. In both, the bleeding was controlled until the bag came out, at which time hemorrhage recurred.

In placenta ablatio we find no use for the bag. The principle of treatment for this pathology, when vaginal delivery is to be undertaken, is to keep the uterus contracted, thus closing off uterine sinuses. A bag increases the size of the uterus, while simple rupture of the membranes with evacuation of all possible fluid accomplishes the desired decrease in size. When pitocin is also given the uterus is kept rather constantly contracted and the termination of labor is expedited. Here again, with the bag, the fetal mortality was 100 per cent, but two infants were premature and the heart sounds were absent in one case at insertion of the bag. The third infant was an anencephalic. Profuse hemorrhage occurred from the fetal head. The Voorhees bag was inserted to speed delivery as the hemorrhage was thought due to a partial separation of the placenta.

As to the second primary indication, i.e., to induce labor, we are not in favor of the use of the bag, except in certain rare instances; one of which would be the presence of a hydrocephalic infant. If the head is in the pelvis, the cervix partially effaced and slightly dilated, and no cephalopelvic disproportion existent, rupture of the membranes, followed by pitocin in small doses, is, we believe, the method of choice. If the cervix is not "ripe" for rupture of the membranes, a complete medical induction will usually prepare it to meet the above requirements. In nine patients labor was induced by insertion of a bag. Six had toxemia. One fetus was dead; one was definitely postmature, and one was a hydrocephalic monster. Only two infants survived; mortality 78 per cent. Fetal heart sounds were absent in only two of the toxemic cases prior to insertion of the bag and these babies were premature, one being nonviable. One of the infants died 48 hours post partum from intracranial hemorrhage.

We believe that the third primary indication, namely, to complete the dilatation of the cervix, is the soundest indication for the use of the Voorhees bag. In many of these instances the Waters type extra-peritoneal cesarean section has been advocated. We, however, feel that this operation should be reserved for those cases in which cephalopelvic disproportion exists and is complicated by mild or moderate infection. The degree of potential or actual infection present in a uterus is exceedingly difficult to evaluate. If one places an incision in a definitely infected uterus, that incision will invariably become necrotic and will

form a focus in which organisms continue to multiply, thereby increasing the hazard to the patient. In frankly infected cases even in the absence of cephalopelvic disproportion, the Porro type section is the procedure of choice. In potentially infected cases without cephalopelvic disproportion, we feel that an intact uterus is a safer uterus, and the Voorhees bag has a definite place in handling this type of pathology. Besides absence of cephalopelvic disproportion one of the following pathological conditions should exist:

- (1) Malpresentation, such as a face, transverse, or double footling.
- (2) Dystocia due to anomalies of expulsive forces or due to cervical pathology with cessation of progress for a reasonable period after labor is established. By progress we mean descent, or increasing effacement or dilatation of the cervix.
- (3) Some threatening complication which necessitates rapid delivery such as a fulminating toxemia, amnionitis, or prolonged rupture of the membranes.
- (4) Some evidence of fetal distress or a prolapsed cord with a viable baby.

There were 27 cases in this group, divided as follows:

#### CASES FETAL DEATH

Prolapsed cord	2	1 (Prolapsed cord on admission)
Fetal distress due to cord interference	4	1
Faulty presentation (transverse, face)	2	1 (Prolapsed arm and cord on admission)
Uterine inertia	19	5

The gross fetal mortality was 29.6 per cent and the corrected fetal mortality 18.5 per cent. Three infants were premature but all survived.

In the 19 cases of uterine inertia, the average length of labor was 48½ hours. The average length of time the bag was in place was 7½ hours, 20 hours being the longest period. There were 5 fetal deaths. One was a hydrocephalic, necessitating craniotomy. In 3 other cases (2 primigravidas) there was a relative cephalopelvic disproportion resulting in "considerable difficulty" at delivery and obvious intraeranian hemorrhage in one infant. Two of these were breech presentations. The cervix was completely dilated by the bag before delivery was attempted. The fifth fetal death was also a breech presentation, in which the bag was removed after 11 hours, with the cervix dilated only 7 or 8 cm. The fetal heart sounds had disappeared. Delivery was accomplished 11 hours later. The 1 maternal death of the series occurred in this group. This patient was a 20-year-old, emaciated, anemic, gravida v, who went into labor at 8 months, after having been in the hospital 4 days for observation. As the cervix was dilated only 3 cm. after 17 hours of labor, a number 4 Voorhees bag was inserted. This was expelled in 4½ hours, following which delivery by version and extraction was performed through an incompletely dilated cervix. A cervical laceration extending into the broad ligament resulted, with hemorrhage and death a few hours later despite hysterectomy. Besides this

case there were five others in which too small a bag was introduced to permit delivery following its expulsion without further measures. These "further measures" were manual dilatation of the cervix, Dührsen's incisions, craniotomy, Braxton-Hicks' version and a two-day delay after which version was performed.

In two instances the bag was unsuccessful: (1) Following insertion of the bag the fetal heart sounds slowed down so markedly that the bag was removed within 15 minutes of its insertion. The infant was stillborn. (2) A large enough bag after being in place 11 hours only dilated the cervix to 7 or 8 cm.

To get satisfactory results with a Voorhees bag we feel that the patient should be in labor and the membranes should preferably be ruptured. The presence of a contraction ring is no real contraindication, for the displacement of the presenting part by the bag tends to overcome this resistance so that delivery can occur or be accomplished.

Our technique for insertion and removal of the Voorhees bag is as follows:

The patient is given an anesthetic and usually by palpation or occasionally by vision, a carefully folded bag is introduced through the cervix. The cervix must be dilated at least 2 cm. or easily dilatable to this point. We feel that a number 5 or 6 bag should be used, preferably the latter. Most of our failures and the one maternal death in this series can be attributed directly to using too small a bag and securing only incomplete dilatation of the cervix, necessitating manual dilatation or incisions to effect delivery. The bag is filled with sterile water, a bandage is attached to the stem and is brought between the patient's legs and over a pulley at the foot of the bed. A weight is attached. We usually use one pound and do not hesitate to increase it to two. Rectal examinations are performed as necessary. When the bag is about to slip through the cervix the patient is put on the delivery table and draped. An anesthetic is administered and only when the patient is anesthetized is the water released and the bag removed. Version and extraction is carried out in most instances.

We realize that the bag has obvious disadvantages, namely, the need of anesthesia for insertion, operative delivery, and possibility of infection. Nine of the 41 patients in this series had a temperature of 100.4° F., or over for two or more consecutive days following delivery, excluding the first 24 hours. One must remember, however, that when the Voorhees bag is employed, the case is a complicated one and the operator is in trouble.

### Conclusions

1. In the absence of cephalopelvic disproportion, the Voorhees bag has a definite place in modern obstetrics.

2. Placenta previa, placenta ablatio, and induction of labor are not primary indications for its use.

3. Its chief use is to complete the dilatation of the cervix, in cases of inertial labor, when progress has ceased; when there is fetal distress from cord interference, or when the cord is prolapsed and the baby viable; when there is an abnormal presentation, or when delivery must be hastened due to a threatening maternal complication.

4. It should be used according to a set technique; a large enough bag should be employed to dilate the cervix adequately, and it should not be removed until the patient is anesthetized and ready for delivery. The delivery should immediately follow in most instances.

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Ramos, A. P., Albertelli, J. F., and Colombo, E.: The Value of Quantitative Determination of Gonadotropin in the Diagnosis of Chorionepithelioma, *Rev. argent. de cien. med.* 1: 8, 1943.

The authors state that the maximum guarantees of early diagnosis of chorionepithelioma are to be found through biologic tests. Since this neoplasm always secretes huge amounts of choriogonadotropins, the quantitative determination of these by-products, in the absence of pregnancy, is of utmost diagnostic importance. For diagnosis the presence of at least 50,000 rat units per liter are required.

The authors conclude that the existence of large amounts of gonadotropin is not essential if re-examinations of urine reveal an ascending curve following an abortion caused by a mole, or if a degeneration of the trophoblast is suspected. They carry out weekly estimates for at least two months, searching for 200 units. If this quantitative determination increases gradually to 500 or 1,000 units per liter the diagnosis can be established and treatment be instituted.

Two outstanding cases which were followed by hysterectomy and pathologic substantiation of the tumor are mentioned in this article.

CLAIR E. FOLSOME.

Matters, R. F.: Sulphonamides and Purulent Peritonitis, *M. J. Australia* 2: 85, 1943.

The author found that intraperitoneal sulfanilamide has proved most effective in cases in which the peritoneum has been infected. It is rapidly absorbed from the peritoneum within 24 hours. The gross pus must be removed before the powdered sulfanilamide is applied. The sulfanilamide does not appear to affect the healing of wounds or the normal state of the intestines.

WILLIAM BERMAN.

## MANAGEMENT OF THE CLIMACTERIC WITH ETHINYL ESTRADIOL\*

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THE climacteric is a syndrome composed of hot flashes, vertigo, irritability, moods of depression, tendencies toward obesity and toward hypertension, premenstrual tension, increased frequency of headaches, and insomnia. Less frequently, leucorrhea, arthralgia, and palpitation of the heart are observed. In varying degrees of severity this syndrome has been noted in most women by the age of fifty. The largest number of healthy climacteric women are but slightly affected. There are, however, gradations in severity such that a significant proportion are notably distressed by this pattern of symptoms. Efficiency appears to be decreased in the most severely affected. The object of this study is to determine the effect of ethinyl estradiol on the climacteric women as evaluated by available objective and subjective criteria.

Prior to the introduction of estrogen for the management of the severe climacteric syndrome, sedatives, tonics, thyroid and psychotherapy have been utilized. The success of these measures has been notably limited, and during the past five years estrogen administration has become the treatment of choice for the severe case. Oral administration was initially achieved by a nonphysiological estrogenic preparation, diethylstilbestrol. In the effective dose range this preparation produced nausea in a sufficient number to invalidate its general employment.

Inhoffen and Hohlweg<sup>1</sup> prepared ethinyl estradiol by means of altering the seventeenth carbon atom in such a manner as to produce a substance approximately fifteen times as active as estradiol, when given by mouth. Proliferative changes in the endometrium were observed by Clauberg and Ustun<sup>2</sup> following a dose of 56 mg. of this preparation which was given over a period of twenty days. Subsequently, Salmon and his associates<sup>3</sup> administered this substance to patients who had climacteric symptoms, which resulted in marked relief. These workers noted that with relatively large doses the vaginal mucosa underwent changes typical of estrogenic stimulation. Moreover, there were some instances of abdominal pain, malaise, chills, vertigo, nausea and vomiting, even though enteric coated tablets were used. It was interesting to observe that when the preparation was dissolved in alcohol all of the patients reported disagreeable side effects.

\*Ethinyl estradiol tablets were donated by Schering Corporation. This study was aided by the Christine Breon Fund for Medical Investigation.

Ethinylated estradiol has been found to be effective following oral administration.<sup>4-6</sup> The required dose has been determined to be quite small. The active portion apparently is slowly released from its ester, thus a continued effect is maintained.

### Procedure

Unselected consecutive clinic patients who presented the symptoms and physical findings of the climacteric syndrome have been investigated by means of basal body temperature determinations, vaginal hydrogen ion concentration readings, and ordinarily endometrial biopsies. When the patient continued to menstruate, the biopsy was taken during the fourth week of the cycle. Detailed subjective reports were recorded for one control cycle, following which the patients were given 50 microgram ethinyl estradiol tablets daily by mouth for courses of twenty-one days. Then there is an interval free from treatment.<sup>7</sup> This free interval usually lasts for one week. Its purpose is to permit the regression of the endometrium and possibly to allow the estrin sensitive tissues to be restored to their optimal effectiveness. Moreover, during this interval, cyclic bleeding can occur. Half of the women found the seven-day interval too long since before it had been completed there was a recurrence of hot flashes. Occasionally one of these who failed to satisfactorily carry through this seven-day interval without estrogen, was given additional tablets in such a manner that the therapeutic plan provided twenty-four days of treatment, then followed a four-day interval without treatment. A modified human assay method along the line suggested by Freed<sup>8</sup> was carried out. In the well-advanced climacteric, bleeding was infrequently seen, in which cases it was customarily scant in amount. In late climacteric cases, bleeding is not desirable. Because of this, the dose of ethinyl estradiol was occasionally lowered to a subthreshold level which was still effective in preventing the vasomotor disturbances.

### Observations

Forty-five women with an average age of forty-six (range thirty-eight to fifty-four) who complained of hot flashes and other climacteric symptoms for an average of 3 years, have been studied prior to treatment for a control cycle, and then through a number of estrogen treated cycles. These varied from three to twenty-four per patient. Three hundred forty-eight treatment cycles compose the basis for this study. Control cycles showed evidence of ovulation in but eight, or 17 per cent of the patients although approximately 55 per cent of the women continued to menstruate. Evaluation of ovulation for the control cycles was made by endometrial biopsies and basal body temperatures in twenty-six patients, and in nineteen by basal body temperatures alone. Of the fifty-five per cent of the patients who continued to menstruate, there was some degree of progestational change in the endometrium during the last half of the control cycles in 17 per cent. The remaining endometrial biopsies showed healthy endometrium with varying degrees of proliferation. The patients had an additional biopsy on completion of six months of treatment. None of these have shown hyperplasia of the endometrium developed during the period of investigation.



Study of the control cycles showed fluctuations in the frequency of the syndrome symptoms at various times, some of them not associated with ascertainable stimuli. The variability between patients also was relatively wide in the objective as well as the subjective standards for the syndrome.

The symptoms and findings before and after treatment with minimal doses of ethinyl estradiol are summarized in numerical form in Table I.

TABLE I. FREQUENCY OF CLIMACTERIC SYMPTOMS IN FORTY-FIVE CASES PRIOR TO AND FOLLOWING ETHINYL ESTRADIOL TREATMENT

SYMPTOMS	BEFORE TREATMENT		FOLLOWING TREATMENT	
	NUMBER	PER CENT	NUMBER	PER CENT
Flashes	45	100	1	2.2
Sweating	42	93	1	2.2
Irritability	40	89	3	6.6
Insomnia	34	76	2	4.4
Vertigo	31	69	2	4.4
Depression	30	66	0	0
Obesity trend	24	53	—	—
Headaches	22	49	4	9.1
Mild hypertension	20	44	—	—
Menstrual irregularity	12	27	2	4.4
Palpitation	11	24	0	0
Leucorrhea	10	22	3	6.6
Arthralgia	10	22	0	0
Nausea	1	2	5	11.

Nine per cent had headaches persist after this minimal treatment. This is in accord with the finding of Groper.<sup>4</sup> Nearly seven per cent had nervousness and restlessness after treatment although the flashes were well controlled. Approximately two per cent of the patients continued to have flashes, although these were decreased in severity and frequency. Attempts to decrease the dosage to 20, 30, or 40 milligrams of ethinyl estradiol daily resulted in the reappearance of flashes in most patients who had been controlled with 50 milligrams. In patients who were accustomed to the occasional use of alcohol it was found that flashes ordinarily appeared the day following its use even though they had taken their customary dose of estrogen. However, doubling the dose as a prophylactic measure on these occasions, tended to restrict the flashes completely.

TABLE II. EVALUATION OF RESPONSE TO 0.00005 GM. ETHINYL ESTRADIOL DAILY

	AVERAGE
1. Age at onset of flashes	46 years
2. Duration of flashes at onset of treatment	3 years
3. Duration of cyclic bleeding following treatment	5.0 days
4. Disappearance of flashes after start of treatment	3.8 days
5. Onset of flashes following cessation of treatment	5.5 days

In this series, as shown in Table II, the average duration of treatment prior to control of the flashes was 3.8 days, while in subsequent cycles the average was decreased to three days. Residual partial saturation with the estradiol might account for this decrease. Upon completion of a 21-day course of estrogen tablets, it was noted that an average of 5.5 days (range one to twelve days) passed before the patient reported recurrence of the flashes.

The hydrogen ion concentration of the midvagina was estimated colorimetrically prior to therapy. The average reading was 5.3, whereas following three weeks of continuous treatment with ethinyl estradiol, the average reading decreased to 4.9. The ranges were 4.8 to 5.8 before treatment and 4.4 to 5.2 after treatment. However, many patients showed negligible change in pH even when the flashes were prevented as a result of the estrogen treatment.

Bleeding under the influence of ethinyl estradiol therapy has lasted somewhat longer than in the nontreated individual. The range varied from no bleeding days to durations of six days. One purpose of the cyclic use of estrogen has been to allow a free interval during which time menstruation may occur. Ethinyl estradiol in the small dose used in this study does not ordinarily cause withdrawal bleeding in women past the menopause, and yet it is effective in suppressing the distressing vasomotor and emotional symptoms. In the menstruating group which included more than half of this series, bleeding during the treatment phase or during the week free from treatment, was not excessive on the dosage employed. There were varying degrees of regularity but no instances of well-defined menorrhagia or metrorrhagia.

While employing a dose of 0.05 mg. of ethinyl estradiol orally each day for three weeks, there has been an incidence of nausea in 11 per cent of the patients. This has been minimal and transitory. There appears to be an increase in nausea with increased doses of this hormone.

Patients having some degree of hypertension seem to have greater unpleasant reactions from their climacteric or after estrogen withdrawal, than do the remaining patients. An arbitrary level of 140/90 under approximately basal conditions, on two occasions, has been accepted as the criteria of hypertension in this study.

### Discussion

Patients having unequivocal climacteric syndromes, such as those following surgical castration, tend to reach an equilibrium after many months without treatment. When ethinyl estradiol has been administered to these individuals, however, there seems to be less severe distress than otherwise obtained during the stabilization period. Control of vertigo, hot flashes, sweating, headaches, the tendency toward hypertension, and a tendency toward obesity, together with irritability, leucorrhea, insomnia, fatigability, numbness of extremities, and menstrual irregularity appeared to be achieved by means of quite small doses of this estrogen. The general condition and subjective feeling of fitness was reported by nearly every patient.

The average vaginal pH changes during ethinyl therapy seemed to have significance in evaluating estrogenation as determined by the colorimetric method. Although inconstant, they were of the order of magnitude of the normal cyclic variation. There was a decrease of an average of 0.4 in the midvaginal secretion observed during treatment with this preparation. However, the hydrogen ion concentration seemed to be less sensitive than the subjective vasomotor reactions in estimating the response to the hormone treatment.

Control of the distressing vasomotor and emotional symptoms of the climacteric has been obtained with this orally active and relatively well-tolerated estrogen. Minimal doses have been effective and side reactions few, none of them of severe degree. Probably the paucity of extraneous reactions is a function of the small dose employed, for when it was increased appreciably the number and incidence of reactions was greater.

### Summary

The climacteric syndrome has been effectively managed in 45 patients through 348 cycles, by means of ethinyl estradiol treatment. This was given in the orally active enteric-coated 50 microgram tablets daily for twenty-one days, followed by a withholding interval of a week's duration. Following six such cyclic treatments, the estrogen was again withheld, this time for a period of one month, and evaluation of the various components of the syndrome was made. Continuation of the therapy was usually indicated. It was not determined whether such estrogen treatment hastens, postpones, or has no effect on eventual symptomatic equilibrium. Transitory sequelae of mild degree occurred at some time during estrogen treatment in 11 per cent of the 45 consecutive patients.

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## ROUTINE ORDER OF EXAMINATIONS FOR THE DIAGNOSIS OF STERILITY

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ONE of the greatest obstacles to the comprehensive analysis of sterility in private practice is the time required by the physician in making the necessary examinations and the consequent prohibitive cost to the patient. Abbreviated diagnostic studies or empiric treatments are as a whole economically, as well as scientifically unsound, and furnish no satisfactory short cut to a comprehensive and well-founded sterility diagnosis. Patients are frequently encountered in private practice who have spent as much as \$200 to \$1,500 for various treatments for sterility without a semblance of a diagnostic study such as here outlined. It seems rather inexcusable. A diagnostic agenda may be considerably simplified by grouping the various examinations in a sequence that is most advantageous both from the diagnostic point of view and the time consumed. To accomplish this, it is necessary that the basic diagnostic examinations of both partners shall be conducted together, in a manner that one complements the other. If not, the picture is apt to be too incomplete to form a basis for a sound diagnosis and prognosis.

The tabulation which follows lists the various examinations in the order ordinarily conducted. References are given to various special technical procedures involved. The entire diagnostic workup requires a single visit by the husband and four visits by the wife. These four visits are usually scattered over a period of three or four months, partly because of therapeutic considerations and partly because examinations and records over a period of several months usually form a much better basis for a diagnosis and prognosis than is possible with a more abbreviated study.

Economies in the time required for the examinations are introduced whenever possible. For Section II, the husband and wife are given a morning appointment for the same day, thus permitting all the laboratory work of this section for both partners to be gotten under way or completed in a single morning. A single sample of blood, some of which is oxalated, permits a complete blood examination, sedimentation rate, corpuscular volume, Wassermann, determination of Rh factor or other tests with the expenditure of only 3 or 4 minutes' time outside the laboratory work. The urine is examined while the patient is resting for the basal metabolic rate and if there is any sugar in the urine, part of the blood sample may be used for a fasting blood sugar determination.

It is usually best to make no pelvic examination at the time of the general medical survey, but rather to defer this to appointments when

TABLE I. TYPE OF EXAMINATIONS FOR STERILITY AND ORDER OF CONDUCT\*

SECTION I. Bottle specimen of semen brought to office by patient first month of diagnostic survey. Patient's presence in office not required.

Observations on semen:<sup>1-6, 8</sup>

1. Amount and physical characteristics.
2. Motility and degree of motility.
3. Density of spermatozoa (number of spermia per cu. mm.).
4. Differential. Type and ratio of pathologic spermatozoa.

\*In individual cases, special circumstances may make it advisable to alter the order given here, but it is usually best to complete any section in its entirety if any of the tests in it are to be done.

SECTION II. Visit by both husband and wife.

Time of examinations—first month of diagnostic survey.

Husband: Length of office visit—3 hours.

1. Urine examination.
2. Basal metabolic rate.<sup>1, 5, 7</sup>
3. Complete blood examination.
4. Blood for Wassermann test.
5. Blood for Rh factor determination if history of miscarriages.<sup>9</sup>
6. Anamnesis.<sup>10</sup>
7. General physical examination.<sup>10</sup>
8. Examination of prostatic smear, including Gram stain.<sup>1, 5</sup>

Wife: Length of office visit—3 hours.

1. Urine examination.
2. Basal metabolic rate.<sup>1, 5, 7</sup>
3. Complete blood examination, including sedimentation rate if history of pelvic inflammatory disease or of any chronic infection.
4. Blood for Wassermann test.
5. Blood for determination of Rh factor and anti-Rh factor if history of miscarriages.<sup>9</sup>
6. Anamnesis.<sup>10</sup>
7. General physical examination (without pelvic examination).
8. Instruction on ovulation timing, basal body temperatures, vaginal smears,\* and other means by which the time of ovulation may be determined. This includes the making of proper graphs or charts.<sup>1, 7, 11, 12, 13, 14, 15</sup>
9. Discussion of the general principles of the treatment of sterility and of the routine handling of the sterility problem.

\*Patient is instructed to take smears on the sixth, twelfth, and twenty-second day of cycle and day of thermal shift, or at other appropriate intervals.

SECTION III. Visit by wife.

Length of office visit—30 to 40 minutes.

Time of appointment, tenth to fourteenth day of cycle—second month of survey.

Scope of examinations and order:

1. Urethral and cervical smear—Gram stain.
2. Vaginal hanging drop if abnormal vaginal discharge. Examined for trichomonads.
3. Vaginal and cervical pH.\*
4. Low and high cervical postcoital examination for spermatozoa (5 to 15 hours postcoitus).<sup>1, 6, 16</sup>
5. Vaginal smear for glycogen (stained with Lugol's solution).<sup>21</sup>
6. Vaginal smear stained for cornification of vaginal epithelium.<sup>1, 13, 14, 15</sup>
7. Pelvic examination.
8. Schiller's test.<sup>1, 19</sup>
9. Intrauterine postcoital examination.<sup>17, 18</sup>
10. Measurement of height of fundus with uterine sound.
11. Uterine insufflation.<sup>10, 20</sup>

\*BDH Universal Indicator or Gramercy Range Finder—Elmer-Amend.

## SECTION IV. Visit by wife only.

Length of office visit—about 30 to 40 minutes.

Time of visit—third month of survey at fertile phase of cycle.

## Order of examinations:

1. Pelvic examination.
2. Vaginal and cervical pH.
3. Vaginal smear stained for cornification.
4. Sperm penetrability.\*
5. 0.5 to 0.7 c.c. of husband's semen injected into the cervix.  
(Semen sample not more than 30 to 60 minutes old.)
6. Intracervical and intrauterine fluid examined for spermatozoa after a lapse of 30 minutes.
7. Recheck of semen analysis from bottle specimen remaining after insemination.

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\*Sample of mucus transferred from cervical canal to microscopic slide. Penetrability to spermatozoa tested by bringing a drop of semen in contact with mucus and observing under the microscope the amount of penetration of mucus.

## SECTION V. Visit by wife only.

Length of office visit—20 to 30 minutes.

Time—Usually twentieth to twenty-sixth day of cycle of third or fourth month of diagnostic survey.

1. Vaginal and cervical pH.
  2. Vaginal smear stained for cornification.
  3. Low and high cervical postcoital examination for spermatozoa.
  4. Pelvic examination.
  5. Schiller's test.
  6. Intrauterine postcoital examination.
  7. Endometrial biopsy.<sup>22</sup>
- 

## SECTION VI. Résumé and correlation of all findings on special analysis sheet given for both husband and wife:

1. Primary diagnosis.
  2. Contributing factors.
  3. Prognosis.
  4. Treatment applied.
  5. Treatment recommended.
- 

the wife is to be on the examination table for other purposes, such as outlined in Section III, IV, and V of the diagnostic survey. While the anamnesis is being taken, the routine blood examination is completed by the technician and the basal metabolic rate calculated. This permits the utilization of information gained from the laboratory work while the patient is still in the office and avoids many repeat visits which might otherwise interfere seriously with the time needed for other cases.

The entire program can be readily carried out in a properly equipped physician's office. No hospitalization is required. Usually a better diagnostic workup is obtained if all of the studies are conducted by a single physician who is particularly interested in the sterility program rather than referring the patient from one specialist to another, many of whom may have little or no interest or experience in the sterility problem as a whole.

Regardless of the group of tests decided upon as constituting a minimal diagnostic sterility agenda, the proper arrangement of examinations will not only facilitate their conduct but will permit a much more comprehensive analysis and a better understanding of the sterility problem than could otherwise be possible.

The omission of such basic tests as those dealing with ovular and spermatie pathology is not uncommon in sterility surveys, and when these or other important basic observations are omitted, a reliable diagnosis is unlikely. Usually, a little advance planning will avoid such omissions without any material increase in time or expense to either patient or physician; and in all but a very small percentage of cases that present some special diagnostic problem, routine examinations for the diagnosis of sterility will be found both practicable and adequate.

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## BREECH PRESENTATION IN THE ELDERLY PRIMIPARA

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**B**REECH presentation has been the subject of numerous contributions in the recent literature, but specific attention has seldom been directed to this type of presentation in the elderly primipara. There have been fifty-five elderly primiparas with primary breech presentations delivered on the indoor service of the Woman's Clinic of the New York Hospital from September 1, 1932, to May 31, 1943. It is the purpose of this paper to review these cases in detail and to give a report of the results found.

In this clinic, a woman thirty-five years of age or over, delivered for the first time of a viable infant, is considered an elderly primipara. During the period of ten years and eight months represented in this study, there were 813 elderly primiparas with viable infants in 29,683 deliveries, an incidence of 2.74 per cent. The incidence of breech presentation in these 813 elderly primiparas is 6.76 per cent. The incidence of breech presentation in the clinic as a whole is 4.72 per cent.

In the group of 55 patients studied 40, or 72.7 per cent, were primigravidas. Nine of the remaining patients had previously had induced abortions, and six had had spontaneous abortions. The number of previous pregnancies were from one to three except in one instance when the patient gave a history of five induced abortions. The 55 patients had a total of 84 pregnancies, 29 or 34.6 per cent of which terminated in an abortion or miscarriage which is a somewhat higher incidence than the usual figure of 20 per cent quoted in the literature. In the entire group only one woman gave a history of relative infertility.

The average age for the 55 patients was 36.9 years; the oldest patient in the study was 42 years. There were 20 private patients, giving an incidence of 36.4 per cent. One patient was colored. There were four sets of twins; the first infant in three sets presented as a breech and in the other set both infants presented as breeches. It is interesting to note that only two, or 3.6 per cent, of the patients delivered on the expected date; 22, or 40 per cent, delivered before, and 31, or 56.3 per cent, after the expected date. The variations from the expected date of delivery were from 60 days before to 30 days after. However, 34 patients, or 61.8 per cent, delivered within a two-week period before or after the expected date. A study of the pelvis in the 55 patients showed an incidence of 12.7 per cent of contracted pelvis as compared to 11.02 per cent in the clinic as a whole.



The following table shows the frequency of antepartum complications of pregnancy in this group as compared with the incidence in the clinic as a whole.

COMPLICATION	INCIDENCE	
	ELDERLY PRIMIPARA WITH BREECH PRESENTATION PER CENT	TOTAL CLINIC PER CENT
Myoma uteri	7.2	1.9
Pyeloureteritis	1.8	1.3
Bleeding in last trimester	1.8	2.3
Toxemia	14.4	11.2
Mild pre-eclampsia	7.2	4.6
Hypertensive disease	3.6	1.2
Unclassified	3.6	1.8
Other types	0.0	3.6

From this table it is evident that the complications of toxemia and myoma uteri are met with more frequently in the elderly primipara group. No patient in this series had syphilis or gave a history of any venereal infection.

In this group of 55 patients, 39, or 70.9 per cent, delivered vaginally. The average duration of labor was 23.8 hours, the shortest labor being 2¾ hours and the longest 86½ hours. Labor was prolonged (30 hours or more) in 21.8 per cent of the cases. In the clinic the incidence of prolonged labor is 9.9 per cent. Sixteen patients, or 29.1 per cent, were delivered by cesarean section. Seven of these patients had some labor prior to the operation, the average duration being 9.4 hours.

A study of the type of the breech presentation shows that frank breech is the most common, 62.5 per cent. Double footling occurred in 10.7 per cent of the cases, single footling and complete breech in 3.4 per cent, respectively, and in 20 per cent of the cases the type was not specified. The most frequent position of the breech was LSA (32.7 per cent); RSA occurred in 27.3 per cent of the cases, and LSP and RSP made up 12.6 per cent of the cases.

Premature rupture of the membranes was noted in 40 per cent of the cases. This means the membranes ruptured before or coincident with the onset of labor. In the clinic a study of 4,250 full-term and premature deliveries of all types showed that the membranes ruptured prematurely in 36.1 per cent of the cases. In Westman's series of 993 breech deliveries, the incidence of premature rupture of the membranes was 32.8 per cent. In spite of the fact that 40 per cent of the patients had premature rupture of the membranes, there were only two patients who developed a puerperal infection. There were no instances of intrapartum infection.

An analysis of the types of analgesia used in the 55 patients shows that nembutal, seopolamine, morphine and rectal ether were used either alone or in combination. However, 30.9 per cent of the patients received no analgesia. The anesthetic administered at the time of delivery was nitrous oxide, oxygen and ether in 83.6 per cent of the cases; the remainder had open drop ether or local, and two patients had no anesthetic.

The following table shows the type of delivery of the 55 patients.

Piper forceps to the aftercoming head were used in 21.4 per cent of the breech extractions, while in the clinic as a whole, the incidence is 14.9 per cent. (External version is not a practice in this clinic.)

TYPE OF DELIVERY	NUMBER OF CASES	INCIDENCE PER CENT
Breech extraction	26	47.3
Decomposition with breech extraction	11	20.0
Spontaneous	1	1.8
Dührssen's incision with breech extraction	1	1.8
Cesarean section	16	29.1
Total	55	100.0

The most outstanding fact in the table is that cesarean section was performed in 16, or 29.1 per cent, of the cases. The incidence of cesarean section in the clinic as a whole is 2.3 per cent, and the incidence of section for the indication of breech presentation is 0.51 per cent. The indications for cesarean section in the 16 cases were as follows:

Acute yellow atrophy of the liver	1
Contracted pelvis	4
Myoma uteri	3
Premature rupture of the membranes	2
Five-year sterility and premature rupture of membranes	1
Previous cerebral accident	1
Breech with extended head	1
Large breech, contracted pelvis	1
Breech presentation	2
Total	16

A post-partum hemorrhage occurred in one of the 55 patients and a manual removal of the placenta was performed. The total morbidity in the series was 18 per cent as contrasted to 9.9 per cent, the total clinic incidence. Premature rupture of the membranes did not appear to be a causative factor in the development of puerperal morbidity, as only two in the 10 febrile cases gave a history of premature rupture of the membranes. Three patients had pyeloureteritis, the febrile puerperium in the others being due to intrauterine infection. There were two maternal deaths, giving an incidence of 3.6 per cent. The mortality rate in the clinic as a whole is 0.198 per cent. Both of these patients died of generalized peritonitis. One was age 38, delivered after 17½ hours of labor by low flap cesarean section, the indication being a contracted pelvis with a large infant. Death occurred on the seventh post-operative day. No autopsy was performed. The other patient was age 36, delivered by classical cesarean section with acute yellow atrophy of the liver as the indication. Death occurred twelve days later. Autopsy showed generalized peritonitis, fatty degeneration of the liver and partial atelectasis.

There were seven infantile deaths in this series, giving an incidence of gross infantile mortality of 12.5 per cent. The incidence in the total clinic for breech presentation is 13.1 per cent. One of the infants, the

second twin of the only instance of both infants being primary breech presentations, weighed 1,570 grams; four weighed between 3,000 and 3,999 grams; and two weighed over 4,000 grams.

The distribution of the weights of the 56 infants (this includes the only second twin presenting by breech) was as follows:

1,500 to 2,499 grams	9
2,500 to 3,999 grams	41
4,000 or over grams	6

The smallest infant in the group weighed 1,570 grams and the largest 4,790 grams. The average weight for the full-term infants was 3,344 grams in comparison with 3,350 grams for the total clinic. It is the opinion of some writers that the elderly primipara tends to have a larger infant.

Two of the infant deaths occurred in patients giving a history of premature rupture of the membranes, and at autopsy the findings suggested death was due to asphyxia. In three of the fetal deaths the mother had received no analgesia during labor. When the histories of the seven infantile deaths are carefully studied, it is noted that all were delivered by breech extraction. Five of the deaths occurred in pregnancies in which labor started two weeks or more past the expected date of confinement, the infants weighing 3,500 grams or over. Labor was desultory and prolonged in these five cases and in two of these a Voorhees bag was inserted to stimulate labor. Three infants were autopsied and the findings were: in the first, multiple small arachnoid hemorrhages; in the second, cephalhematoma and tentorial tears; and in the third, subcutaneous and petechial hemorrhages. Six of the infants were deadborn and macerated at delivery, the seventh one died of prematurity, shortly after birth. The fetal heartbeat was lost in three instances in the first stage of labor, in one case just before delivery, and in three others before the onset of labor. Among the 49 infants discharged well, only one had required resuscitation following delivery, one infant had a subarachnoid hemorrhage, one had a fractured humerus, and one developed hemorrhagic disease.

### Discussion

The elderly primipara with a breech presentation at term is a serious problem that requires careful study of the patient. Accurate pelvic measurements should be obtained and x-ray pelvimetry employed when possible. When the patient is to be delivered vaginally it is not advisable to interfere with the progress of labor by attempts to speed it up. The most unsatisfactory types of labor and poorest results occurred in patients delivering two weeks or more past the expected date of confinement. Elective cesarean section is favored in cases of a large infant, patients overdue two weeks or more with a large infant, and when there is a history of sterility or of repeated spontaneous abortions. Cesarean section should not, as a rule, be the operation of choice when there has

been a desultory type of labor with premature rupture of the membranes or after vaginal manipulation. If a section must be done in such cases, the extraperitoneal type should be performed.

### Conclusions

1. The incidence of breech presentation in elderly primiparas is 6.76 per cent as compared with 4.72 per cent, the incidence of breech presentation in the clinic as a whole.

2. The incidences of toxemia and myoma uteri are increased in the elderly primipara group, being 14.4 per cent and 7.2 per cent, respectively, as compared to 11.2 per cent and 1.9 per cent for the same complications in the total clinic cases.

3. Premature rupture of the membranes occurred in 40 per cent of the elderly primipara group, while in the clinic as a whole it occurred in 36.1 per cent of the cases.

4. There were two maternal deaths in this group of 55 elderly primiparas, giving an incidence of 3.6 per cent for maternal mortality. Both of these patients had a cesarean section, the indications being contracted pelvis with a large infant and acute yellow atrophy of the liver, respectively. The final diagnosis in each patient was generalized peritonitis.

5. The incidence of gross infantile mortality was 12.5 per cent.

6. Cesarean section is indicated in the elderly primipara with breech presentation associated with any one of the following: Large infant, contracted pelvis causing dystocia, myoma uteri, patient two weeks or more past term with a large infant, repeated spontaneous abortions, or a history of sterility.

## GRANULOMA PYOGENICUM OF THE CERVIX

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GRANULOMA pyogenicum of the skin is not a rare disease, and occasionally the condition occurs on the lips, tongue and buccal mucosa. Rarely the conjunctiva, bladder or other mucosal surfaces are involved. Reasoning along anatomical and physiological lines, one would expect to find cases occurring in the cervix and vagina, but a careful search of the gynecological literature reveals no reference to this condition. A typical case of granuloma pyogenicum involving the cervix uteri and associated with a marked decidual reaction appears therefore to warrant a brief report.

The disease was first described in 1897 by Poncet and Dor,<sup>1</sup> who designated the condition "botryomycosis humaine." This name was given it because of the similarity of certain mulberry-like masses found in the tumors to those which had been described by Bollinger in the inflammatory scrotal tumors which frequently follow castration in the horse. It was later shown that the mulberry-like masses are not constant in the lesions of this disease and that the most likely causative agent is the ordinary *Staphylococcus aureus*. In 1904 Hartzell<sup>2</sup> proposed the term "*granuloma pyogenicum*," which has been generally adopted in the dermatological literature.

Granuloma pyogenicum is a localized disease of organs covered by squamous epithelium, and not infrequently it follows slight trauma. It is seen most frequently on the hands, fingers, feet, face and buccal mucosa. The lesions are usually single and consist of sessile or pedunculated bright red, inflammatory tumors which vary in diameter from a few millimeters to about 3 cm. They bleed easily and not infrequently emit a foul odor.<sup>3</sup>

The process begins in the subepithelial connective tissue and is characterized by the formation of ordinary granulation tissue which rapidly elevates the epithelium in such a manner as to form a small nodule or tumor on the surface. As the disease progresses, the epithelium is destroyed and granulation tissue grows above the surface, forming a sharply demarcated inflammatory tumor.<sup>4</sup> The lesions are fully formed in the course of a few weeks after their inception.

The skin lesions can be completely cured by wide excision or by the use of carbon dioxide snow. Large tumors are usually treated with roentgen rays, however, since the lesions are very radiosensitive.

Since the tumor of the cervix which we are reporting is identical in every respect with the classical cases of granuloma pyogenicum occurring on the skin, a more detailed description of the microscopic anatomy will be given in the case report.

### Case Report

A 21-year-old white, married female consulted Dr. J. L. Pressly of Statesville, N. C., on August 2, 1943, requesting prenatal care. Her menses had been established at the age of 12 years and occurred every twenty-eight days, with a duration of five days. There had been one previous pregnancy, which was normal in every way and terminated with the delivery of a normal baby in February, 1942.

Her last menstrual period was on Dec. 26, 1942, and her prenatal course was uneventful until March, when she noted slight vaginal bleeding. Examination at that time revealed nothing of consequence, and the source of the blood was not established. The bleeding ceased spontaneously in a few days and did not recur until September 13, when she began to bleed profusely. She consulted her physician, who found a rather brisk flow of bright red blood coming from the vagina.

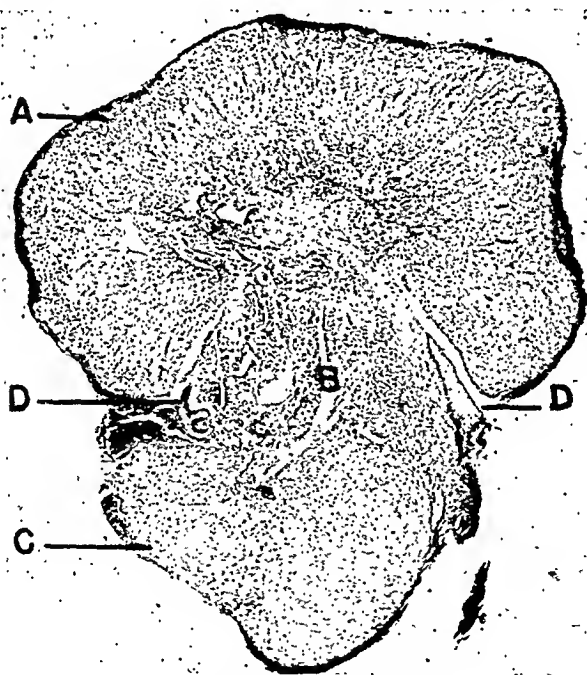


Fig. 1.—The entire lesion. A. The inflammatory tumor. B. Stalk of tumor. C. Decidual tissue. D. Squamous epithelium. ( $\times 13$ .)

Vaginal examination by Dr. T. V. Goode revealed, on the posterior lip of the cervix, a bright red growth which was elevated about 8 mm. above the surface and measured 1 cm. in diameter. It was excised widely, placed in 10 per cent formalin solution, and sent to this laboratory for examination.

The patient was delivered on September 13, and had an uneventful puerperium with no evidence of recurrence of the lesion.

#### *Microscopic Examination:*

Sections through the entire mass (Fig. 1) show a pedunculated tumor (Fig. 1-A) possessing a rather broad stalk (Fig. 1-B) which is con-

tinuous with irregular accumulations of chronically inflamed decidual tissue in the deeper portions of the cervix (Fig. 1-C). On either side of the stalk is a small piece of stratified squamous epithelium (Fig. 1-D), which now occupies a vertical position. One gets the impression of epithelial elevation, followed by destruction and extensive growth above the surface. The inflammatory tumor is composed of prominent and numerous capillaries surrounded by proliferating fibroblasts, neutrophils, plasma cells, monocytes, lymphocytes, eosinophiles, mast cells and fibrin (Figs. 2 and 3). The neutrophile is the predominating cell,



Fig. 2.—Granulation tissue and inflammatory cells. ( $\times 90$ .)

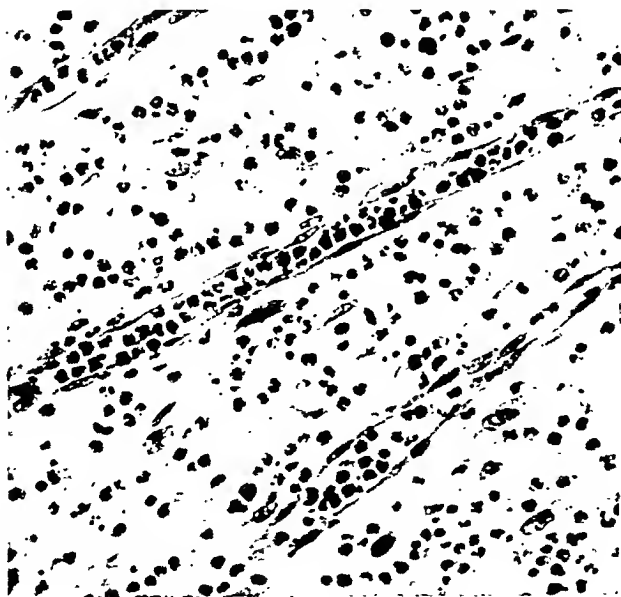


Fig. 3.—Same as Fig. 2. ( $\times 320$ .)

and many young forms are present. On the surface, the tissue has become necrotic and large numbers of neutrophils in all stages of degeneration are present. The capillaries radiate from the stalk to the periphery of the lesion and are filled with inflammatory cells.

The stalk of the tumor is composed of smooth muscle and collagenous connective tissue, along with numerous blood vessels and large accumulations of plasma cells (Fig. 4). Many of the latter are multinucleated, while others can be seen in the various stages of mitosis. The stalk is continuous with irregular sheets of decidua which are infiltrated by a moderate number of plasma cells and neutrophils (Fig. 5).

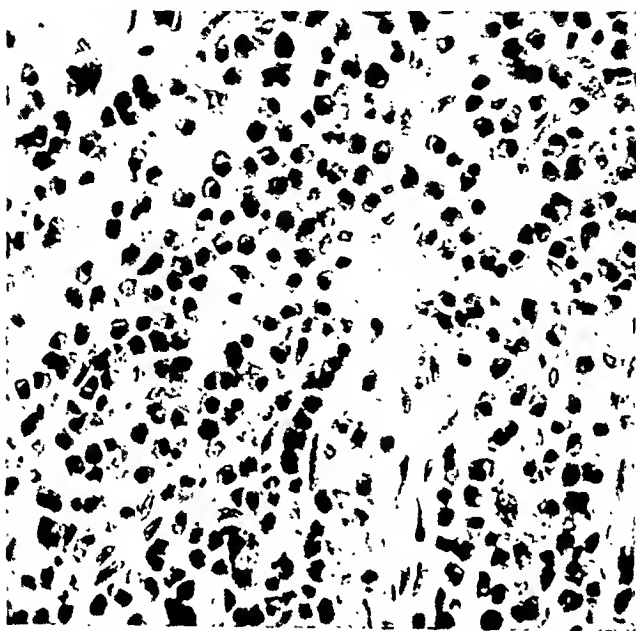


Fig. 4.—Plasma cells. Note that several are multinucleated. ( $\times 320$ .)

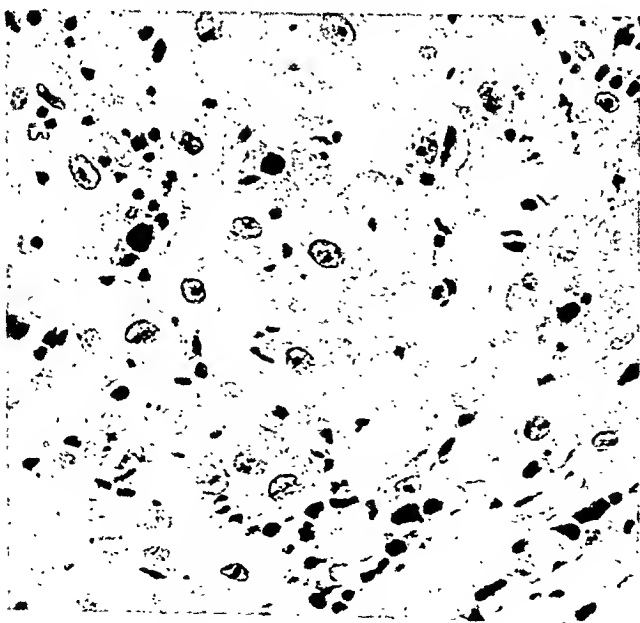


Fig. 5.—Decidual tissue. ( $\times 320$ .)



### Comment

This case is of interest for several reasons. In the first place, it affords an opportunity to study thoroughly a heretofore unrecognized cervical disease. Secondly, it presents an additional example of a rather pronounced decidual reaction in the cervix, which is of extremely rare occurrence. It is of interest still further since it affords an opportunity for speculation as to a possible relationship between the two processes.

We are unable to state with certainty that any relationship exists between granuloma pyogenicum of the cervix and pregnancy. However, the imbibition of the cervical tissues associated with pregnancy may provide a more fertile soil for the staphylococcus, which, in all probability, is the causative agent in this condition. Latzko<sup>5</sup> has pointed out that, although frank decidual reactions in the cervix are extremely rare, they are sometimes observed in connection with markedly inflamed polyps. It is possible that many of the polyps reported in this connection represented in reality examples of granuloma pyogenicum which had been wrongly diagnosed. This erroneous diagnosis may have been due to the examiner's unfamiliarity with the disease, or to the condition of the specimen at the time of its arrival in the laboratory.

The diagnosis of granuloma pyogenicum should be made clinically, for the lesions are very characteristic. If the pathologist is fortunate enough to receive the entire tumor, the microscopic picture is also pathognomonic, but if the specimen is received in a fragmentary or distorted condition, the diagnosis is likely to be missed.

### Conclusions

A case of granuloma pyogenicum occurring in the cervix uteri and associated with a pronounced decidual reaction in that organ is reported. It is probable that the condition is of fairly frequent occurrence, is closely related etiologically to the cervical softening of pregnancy, and is especially likely to appear in the rare cases of gestation which are associated with a frank decidual reaction in the cervix.

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## ECLAMPSIA, CEREBRAL ABSCESS AND HEMORRHAGE\*

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ECLAMPSIA, the convulsive toxemia of pregnancy, is characterized by the appearance of edema, hypertension, albuminuria, and convulsions in a pregnant, parturient, or puerperal woman previously free from such symptoms. The etiology of this acute toxemia which has, in the course of time, been ascribed to all manner of causes, both maternal and fetal, is still nebulous. Inasmuch as convulsions and coma are an integral part of the disorder, the differential diagnosis must often include the consideration of intracranial lesions of inflammatory, neoplastic, and vascular origin. The clinical confusion is heightened by the fact that the recurring eclamptogenic convulsions may take on a more localized than a generalized character because of the secondary occurrence of cerebral hemorrhage. The latter is found in approximately 10 per cent of the patients dying from eclampsia.

The following case history illustrates the pitfalls that may be encountered in the differential diagnosis of eclampsia and raises a question concerning the improbable etiologic relationship of eclampsia to a space-taking lesion of the midbrain.

Mrs. S. R. (St. Luke's and Children's Medical Center No. 17271), white, schoolteacher, twenty-seven years of age, thirty-two weeks' pregnant, was admitted to the Hospital during the evening of February 2, 1943, because of a sudden convulsion followed by coma.

The patient had first come under observation three years earlier, in 1940, when she sought contraceptive advice. It is significant that, at that time, the patient had complained of recurring headache of several months' duration, a complaint which persisted and was subsequently attributed to "chronic sinusitis." Except for this long-standing history of headache and an appendectomy at the age of 17, the patient's past medical background held no special interest. A planned pregnancy was initiated during the summer of 1942, the last menstrual period occurring on July 1. The progress of the pregnancy was normal and uneventful, both as reported by the patient and as observed during office examinations on September 15, October 13, November 10, and November 24. The blood pressure, weight increment, urinalysis, and uterine enlargement were perfectly normal at each of these visits; the blood Wassermann reaction was negative. On November 28, at approximately the twenty-second week of gestation, the patient went to Florida for ten weeks, during which period she visited a physician and was pronounced well on three occasions.

The patient returned to Philadelphia during the afternoon of February 2, 1943, stating that she had begun to suffer increasingly severe headache and edema two days earlier. Three hours after her homecoming, she experienced a sudden convulsion, described as "generalized" by lay witnesses, and subsequent coma of one hour's duration.

\*Presented at a meeting of the Philadelphia Obstetrical Society, October 7, 1943.

During the latter period, she was seen by a physician who noted the presence of almost universal, pitting edema and found the blood pressure to be 164/118.

At the time of hospitalization, 8 P.M., February 2; the patient was conscious, exhibited evident edema of the face and limbs, had a blood pressure of 148/112, and complained of headache. A specimen of urine, obtained by catheterization, showed a dense cloud (four plus) of albumin. The uterus extended to three fingerbreadths above the umbilicus, the presentation was a vertex, and fetal heart tones were clearly audible. The treatment administered on admission included 10 c.c. of a 20 per cent solution of magnesium sulfate intramuscularly, 100 c.c. of a 50 per cent solution of glucose intravenously, one-quarter grain of morphine sulfate hypodermically, a soapsuds enema, gastric lavage until clear, and 2 ounces of a saturated solution of magnesium sulfate orally. Despite an evident oliguria, the patient improved during the night—the edema was notably less, the blood pressure fell to 136/106, and the headache was alleviated. Labor, induced by rupture of the membranes, began at 6 P.M., February 3, was normally progressive, and was terminated 15 hours later—9 A.M., February 4—with the spontaneous birth of a living, male child in very poor condition. The baby, 15 inches in length and 2 pounds, 12 ounces in weight, lived but one hour.

The patient's immediate post-partum course was afebrile and, aside from the frequent complaint of headache of the left frontal area, was uneventful. The daily blood pressure readings ranged between 100/70 and 140/90, the albuminuria disappeared, and a complete laboratory survey of the blood chemistry and blood count revealed no abnormalities. Thorough examination of the nasal sinuses failed to reveal signs of infection as a cause of the persisting headache. The patient was out of bed on the ninth post-partum day, February 12. That evening she appeared to be abnormally drowsy. The following day, February 13, the patient's headache was more severe, weakness of the right arm was noted, and drowsiness was evident. A day later, February 14, a neurological examination disclosed slight nuchal stiffness, bilateral Kernig's sign, and a definite hemiparesis of the right side. The clinical impression, then, was that the patient had either a moderate subarachnoid hemorrhage or cerebrovascular spasm as a result of the eclampsia. Treatment included 20 mg. of thiamin chloride and 100 mg. of niacinamide intravenously daily, as well as one-quarter grain of papaverine orally three times daily. A lumbar puncture, performed on February 15, yielded 12 c.c. of clear, distinctly xanthochromic, cerebrospinal fluid which was shown to contain 600 erythrocytes and 800 leucocytes (chiefly polymorphonuclears) per cu. mm. On February 16, the patient was deeply stuporous. Neurological examination revealed the signs of a left cerebral lesion, presumed to be either hemorrhage or an acute encephalitis as a result of an infected embolus. There was little to support the latter diagnosis, inasmuch as the patient was afebrile, had no leucocytosis, and presented perfectly normal genital organs.

The patient never roused again. She was supported by means of gavage feedings, and was given 100 c.c. of 50 per cent solution of dextrose and 10 mg. of vitamin K intravenously twice daily. She expired on February 20, the sixteenth post-partum day. A retrospect study of the clinical record uncovered the significant fact that, during the last week the patient had a distinct bradycardia, the axillary temperature being fairly steady at 99.5° F., and the pulse rate being 60, with occasional drops to 50, per minute.

*Post-mortem Examination.*—The only organ which showed relevant changes, at autopsy, was the brain. It is significant that the pelvic organs were entirely free from signs of infection and that the liver, on histologic study, was devoid of periportal hemorrhage and necrosis, the lesions so characteristic of eclampsia.

The brain was large. The frontal section showed a fresh abscess involving the left frontotemporal area, beginning at the level of the anterior pole of the lateral ventricle and extending from the posterior part of the frontal lobe throughout the entire extent of the temporal lobe. The abscess cavity measured 3 by 9 by 2 cm. It had a poorly defined wall and practically no capsule, giving the impression that it was acute. The abscess lay deep under the cover of the insula, and involved the region of the left lenticular nucleus adjacent to the internal capsule. It had destroyed the left thalamus and the posterior limb of the internal capsule. The anterior portion of the abscess contained pus and blood. On its medial aspect, adjacent to it, was a recent hemorrhage involving the internal capsule and basal ganglion.

A culture of the pus in the abscess cavity yielded a growth of pure pneumococcus.

### Comment

The history of a twenty-seven-year-old, white female is related, delineating the occurrence of eclampsia at the thirty-second week of gestation, followed by the premature birth of a child who lived but one hour. The post-partum course of the patient was noteworthy because of the appearance of coma, right hemiparesis, and death. The autopsy disclosed the presence of a large cerebral abscess and an adjacent area of hemorrhage.

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## ERYTHROBLASTOSIS FETALIS IN IDENTICAL TWINS

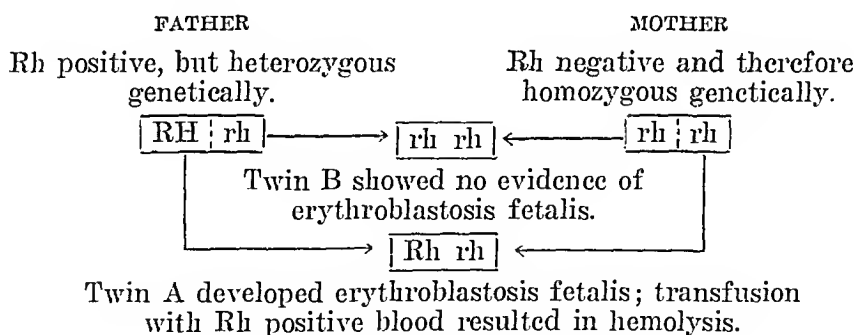
NICHOLAS GEORGE DEMY, M.D.,\* NEW YORK, N. Y.

(From the Department of Obstetrics of the New York Polyclinic Hospital)

**A**LTHOUGH we are quite certain that the cause of erythroblastosis fetalis has its inception in genetic differences between the mother and father, there is by no means complete agreement in its mode of transmission. According to Levine, no great number of red cells is necessary to sensitize the mother provided the proper Rh factor conditions are present, and that such a number can be accounted for on the basis of diapedesis alone. Placental defects characterized by infarcted areas and the persistence of Langhans' cells have been described. The origin of these defects is unknown; capillary fragility from avitaminosis C has been postulated though the case to be described would throw doubt on this assumption.

Not every union of an Rh positive father and an Rh negative mother results in erythroblastosis fetalis, nor are the clinical pictures in the infant identical in every case, so that the placenta does figure in its pathogenesis. The differing prognoses in icteric, anemic, hemorrhagic, and hydropic forms indicate varying degrees of sensitivity and levels in the titer of antibody in the mother.

Kariher reported in the July 31, 1943, issue of the *Journal of the American Medical Association* a case of erythroblastosis fetalis in one of double ovum twins, the other being normal. The affected twin was transfused with the father's blood and died. Since the Rh positive factor is a Mendelian dominant, the following scheme probably represents the mechanics in this case:



The present case resulted in a forty-year-old gravida vii, para vii, who had had four successive living infants in 1924, 1927, 1929 and 1932. In 1934, she gave birth to twins, one of whom was stillborn; the other lived four hours, dying of hemorrhage. In 1936, she gave birth to a sixteen-pound stillborn child, and though no data are available other than that hemorrhage was present, we may assume this to have been a case of fetal hydrops. Erythroblastosis fetalis was suspected in the present gestation, and a diagnosis of twins was made before delivery. The father's blood proved to be Rh positive; the mother's Rh negative in high titer. Labor resulted in the normal spontaneous delivery of living twin girls. There

\*At present in Service with the Armed Forces.

were a single placenta, single chorion and two amnions so that these were identical twins. Microscopic examination failed to reveal anything abnormal.

Twin A weighed 5 pounds, 8 ounces, and was jaundiced at birth, petechial hemorrhages appearing all over its body within twenty-four hours. Its spleen and liver were greatly enlarged and hard. Blood count on the first day:

R.B.C. 1,560,000, Hemoglobin 40%, W.B.C. 164,000, Pmn. 49%, Lymphocytes 47%, Myelocytes 2%, Metamyelocyte 2%, Polychromatophilia: Marked, Achromia: Marked, Anisocytosis: Moderate, Poikilocytosis: Moderate, 321 Normoblasts/100 W.B.C., 27 Megaloblasts/100 W.B.C.

One hundred c.c. of blood from an Rh negative male donor were given into the anterior fontanelle. Intramedullary transfusion was unsuccessful probably due to hyperplasia of the marrow. A count on the second day showed:

R.B.C. 3,160,000, Hemoglobin 68%, W.B.C. 26,600, Pmn. 68%, Lymphocytes 24%, Eosinophiles 1%, Myelocytes 2%, Metamyelocyte 2%, 55 Normoblasts/100 W.B.C.

A second transfusion of eighty c.c. was given into a scalp vein. The count following this was:

R.B.C. 4,190,000, Hemoglobin 81%, W.B.C. 4,400, Pmn. 67%, Lymphocytes 25%, Myelocytes 6%, Metamyelocyte 2%, 49 Normoblasts/100 W.B.C.

Subsequent counts were within normal limits. One week after delivery the icterus index was 85. Since the child was not doing well despite the normal counts, another transfusion of ninety c.c. was given followed in three days by an additional one hundred c.c. Vitamin K, copperin B and liver extract were given empirically. On the fifty-first hospital day, twin A was discharged with a deep mahogany-colored skin, slightly enlarged liver and spleen and a weight of 6 pounds 4 ounces.

Twin B weighed 5 pounds, 14 ounces at birth, and was also jaundiced though to a much lesser degree. Spleen and liver were not remarkable. Blood count on the first day:

R.B.C. 4,550,000, Hemoglobin 90%, W.B.C. 21,600, Pmn. 72%, Lymphocytes 24%, Myelocytes 4%, Poikilocytosis: Moderate, 34 Normoblasts/100 W.B.C.

One hundred c.c. of Rh negative blood from a male donor were transfused into the anterior fontanelle. Blood count on the third day:

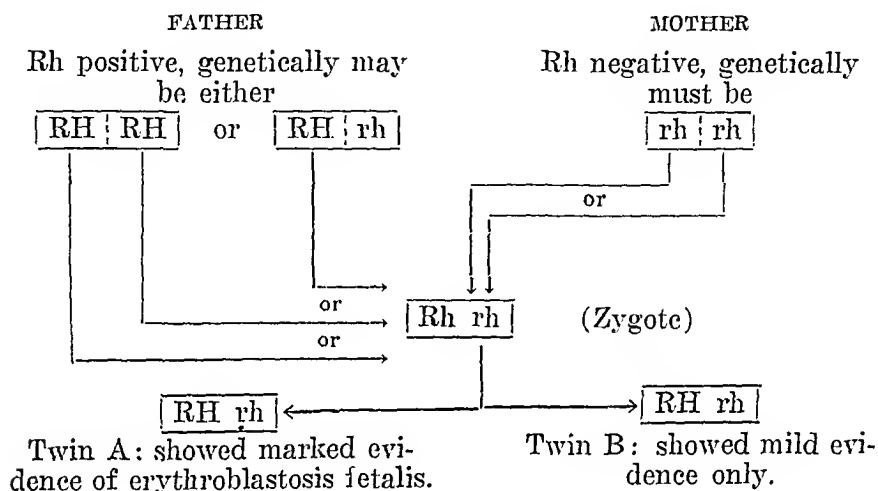
R.B.C. 4,000,000, Hemoglobin 79%, W.B.C. Q.N.S, Pmn. 36%, Lymphocytes 50%, Myelocytes 8%, Metamyelocytes 6%, 40 Normoblasts/100 W.B.C.

It was also given vitamin K, copperin B and liver extract but no further transfusions. Subsequent counts were normal. On the fifteenth hospital day, it was discharged weighing, 5 pounds 12 ounces. Latest report is that they are both doing well and thriving.

### Comment

It is not certain whether the father is genetically hetero- or homozygous since the first four normal offspring might have occurred in the absence of a placental defect, lack of sensitization of the mother, or low titer of antibody. The last pregnancy resulted in single ovum twins, so that they had identical genetic inheritance, were both Rh positive and

therefore subject to the same titer of antibody from the mother; yet one developed a severe hemorrhagic form of the disease whereas the other reacted only mildly and might have escaped notice were it not for the history of the case and the condition of its twin. One can only conclude that the portion of the placenta serving twin A had a greater functional defect than that serving twin B, resulting in more massive exposure to antibodies from the mother. The following is probably the sequence in this case:



## A CASE OF INCARCERATED UTERUS SUCCESSFULLY TREATED IN 1808

HERBERT THOMS, M.D., NEW HAVEN, CONN.

**I**NCARCERATION of the pregnant uterus is not a common complication of pregnancy. When present it can usually be successfully treated by modern methods even if laparotomy has to be resorted to. However, previous to our time, before the development of aseptic techniques, the successful treatment occasionally offered many difficulties. In reviewing the present case we are reminded of another instance in the annals of medical history the significance of which was truly great. This was the celebrated case of Mrs. Merrill of Montgomery, Alabama, who was successfully treated by Dr. J. Marion Sims. It will be recalled that the invention of the Sims speculum and the development of a cure for vesicovaginal fistula were the direct result of Sims' experience, and when we consider his eminent and spectacular career from that time forward, we are inclined to hazard a view that Mrs. Merrill ought also to have her niche, even if a small one, beside her famous compatriot Jane Crawford.

The case here reprinted is interesting from two points of view: first, because of its early record and, second, because of the method used in its successful treatment. It was apparently the author's wish to remain anonymous, for he chose to sign his contribution, "A Member of the Society," and a cursory search has not revealed his identity. He remains, therefore, as he wished it, unknown. The story begins in the year 1809, when, at a Convention of the Fellows of the Medical Society of the State of Connecticut a committee was appointed to select pieces for publication from such communications as were then in the possession of the Secretary and publish them before the meeting of the next convention. The result was the publication in 1810 of a collection of fourteen papers, all of which were signed except the one referred to here. Among the authors we find names notable in American medicine. Lemuel Hopkins, a pioneer in the treatment of tuberculosis and a "Connecticut Wit," Eli Ives, a founder and professor of the Yale Medical School and one time President of the American Medical Association, and William Tully, "unrivalled in his knowledge of the *materia medica*" and important as a medical educator. The final item in the Table of Contents is a Case of Retroverted Uterus and appears as follows in the text:

*"The following case of retroverted Uterus may be important, on account of the simple means used to restore the Uterus.*

"September 23, 1808, Mrs. A----- of New Haven, a woman of forty years of age, the mother of eight children, in jumping from a horse, felt something give way in the pelvis; at this time she supposed herself to be about three months advanced in pregnancy. The shock was followed by great weakness; sensation of bearing down, costiveness, dysuria, nausea, and vomiting, and all the train of hysteric symptoms, arising from the stomach, sympathizing with an irritating and inflamed uterus. These symptoms were supposed by the patient to arise from her pregnancy, and of course were endured with patience, until they increased to a very alarming degree. A period of fifteen days elapsed, during which she took a



little castor, valerian, etc. At this time she was examined. Entering the vagina, the finger met a tumor twice the size of a hen's egg, between the vagina and rectum, pressing itself forward into the vagina, and occupying two-thirds of the os externum. A finger of the other hand was passed into the rectum, by which it appeared that this tumor was a sack of the rectum filled with indurated feces, which sack had been formed by the pressure of the superincumbent uterus; passing the finger into the rectum, a little farther up, the rectum was entirely obstructed by the fundus of the uterus, beyond which the finger could not pass, and on which it could make no impression. The uterus at the same time was felt by the finger in the vagina, wedged firmly between the sacrum and pubis and the os tincae, in the superior and anterior parts of the vagina. At this time the stomach could retain nothing—strong spasms agitated the system frequently; bowels were full and tense, particularly above the pubis; frequent inclination to pass urine and stool, with much pain and distension in the pubis. The urine had been entirely obstructed; but for two or three days past the patient thought she had passed the usual quantity of urine; however, the catheter was introduced, and eight pounds and three ounces of urine drawn off. The rectum was also emptied. The patient was laid upon her back, her hips raised; in this position, with two fingers in the vagina, and two in the rectum, exertions were made to restore the uterus, until her physicians were satisfied that it could not be restored in this manner. The patient was placed on her knees and elbows, and repeated trials made to restore the uterus, but with no better success. The uterus was finally restored by an instrument resembling a probang, made of a cylinder, the size of the finger, and eight or ten inches in length, on the end of which a head was formed, by winding flax and covering it with soft leather, as large as could be passed into the rectum. With this instrument, oiled and introduced into the rectum, the patient on her knees, the thorax lower than the pelvis, two fingers in the vagina, and much force applied by the instrument and fingers, the uterus was raised above the brim of the pelvis. The patient was enjoined rest and a recumbent posture; and after the usual period of gestation, was delivered of a healthy child.

“New Haven, July 10, 1810.”

“A Member of the Society.

In the above case it will be seen that the author first used without effect the technique later successfully applied by Sims. It remained, therefore, for him to exercise an ingenuity which he probably came by through his Yankee forbears.

## UTERUS BICORNIS UNICOLLIS WITH ASSOCIATED STERILITY CORRECTED BY SURGERY\*

J. R. EISAMAN, M.D., PITTSBURGH, PA.

**B**ECAUSE of infertility during six years of married life, Mrs. B. (No. 60097) sought medical advice in December, 1940. She was then 32 years of age and had never been pregnant.

Her general physical examination, health and habits were normal. Laboratory and endocrine studies were also normal. Her husband was well, sexually potent and fertile as judged by Hühner test and seminal analysis. However, what was thought to be a small fibroid was detected to the right of the cervicofundal junction of the uterus. This tumor was not larger than  $1\frac{1}{2}$  inches in diameter.

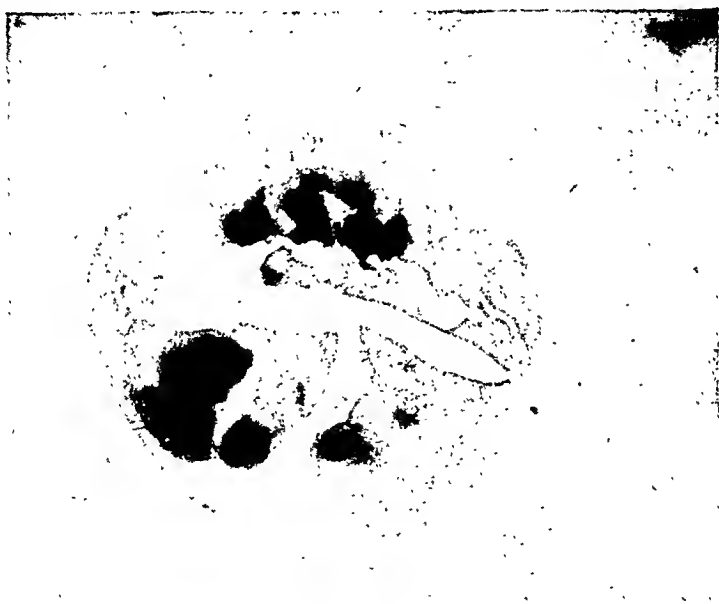


Fig. 1.—Position of uterine cornua before operation.

In April, 1941, after some months of effort on the part of Mrs. B., her husband, and her physician, it was decided to remove the one possible cause of her sterility, the *small fibroid*. She was admitted to a hospital for operation. Fortunately, the uterus was injected with iodized oil before laparotomy and a bicornuate uterus was apparent. Because of the extreme lateral flexion of the uterine horns, a stem pessary was inserted into the right side of the uterus in June, 1941, and retained for 6 months.

About March, 1942, her family physician found tenderness about her right lower abdominal quadrant and suggested an appendectomy. The operation was duly performed and an incidental uterine plastic opera-

\*Read before the Pittsburgh Obstetrical and Gynecological Society, Dec. 6, 1943.

tion also was done. This consisted of stripping the peritoneum from the superior surfaces of the uterine horns, approximating the organs and anchoring them with silk sutures. By so doing, the component parts of the uterus were brought into an upright and more normal position.

After a rather short interval at home she complained of amenorrhea and a positive Friedman test was obtained. As prophylactic measures, wheat germ oil, corpus luteum (orally and intramuscularly) were administered and continued until the fetus was viable.

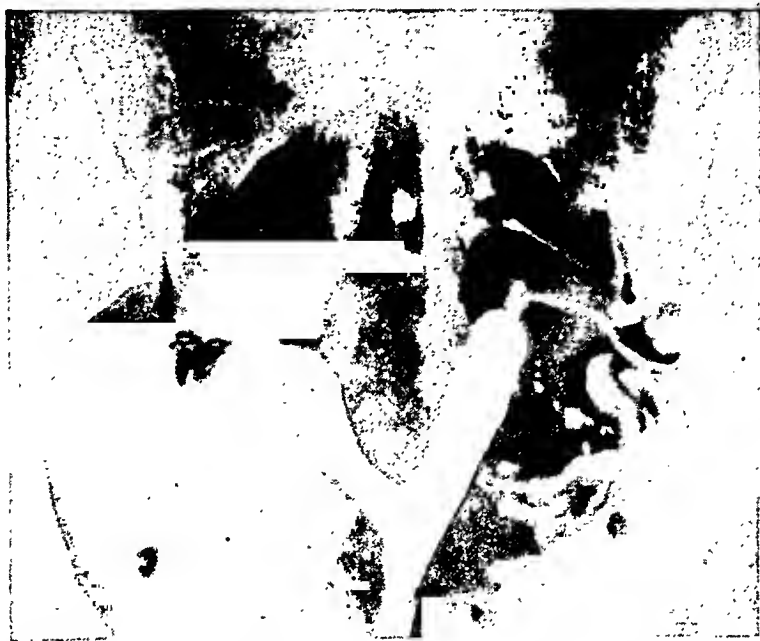


Fig. 2.—Relative position of cornua ten weeks after delivery of infant from larger right horn.

In August, 1943, she was admitted to the hospital, one week before the expected date of confinement, to be prepared for cesarean section. The day before operation was planned, an inertial labor began and a low classical cesarean operation was done, after a labor of four hours. At operation the fetus was found within the right cornu of the uterus, the left remaining quite distinct but closely attached to the other. A 7-pound 3-ounce living male infant was delivered. The placenta did not separate spontaneously after the use of intravenous pitocin. When removed manually, it was found to be attached to the mesial surface of the right cornu. The myometrium of this horn was noted to be flabby and so thin that the gloved hand was apparent through the wall.

Although this case is interesting because of the apparent effectual relief offered to this patient by partial correction of the uterine anomaly, it is not unusual as this condition is reported to be found once in every 1,500 obstetrical and again in every 2,000 gynecological cases.

# Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

## ADVANCES IN ENDOCRINE THERAPY\*

ROBERT T. FRANK, M.D., NEW YORK, N. Y.

ENDOCRINE therapy is one of the newest branches of medicine. Its scope is enlarging and changing constantly. Almost daily new claims are made and previously current procedures discarded. In what follows, I shall present to you what I consider sound practice as of today.

An attempt at endocrine therapy was made in 1889, when the famous, peripatetic physiologist, Brown-Séquard, described the rejuvenescent effects of a crude testicular extract which he had prepared and used upon himself. Many years passed before effective androgenic therapy was developed, but in the interim his example was followed by numerous imitators.

Effective endocrine therapy may be said to have originated in 1891, a mere fifty-two years ago, when Murray used a glycerin extract of fresh sheep thyroid glands upon a woman afflicted with severe myxedema. Shortly thereafter he changed to desiccated thyroid substance, a remedy which we still use. As a result of this striking success, the lay public since has been fed, *ad nauseam*, with desiccates of all the endocrine glands, as well as with splenic, mammary, placental and prostatic substances.

TABLE I CHRONOLOGICAL REVIEW

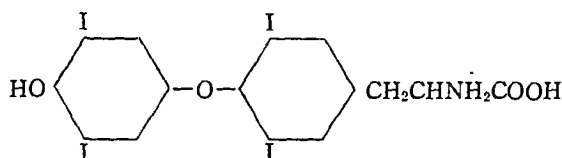
1891	<i>Thyroid Extract</i>	Murray
	1914—Thyroxin	Kendall
1895	<i>Pituitrin</i>	Sharpey-Schafer
	1928—Pitocin, Oxytocin	Kamm
1901	<i>Epinephrine</i>	Aldrich, Takamine
1922	<i>Insulin</i>	Banting and Best
	1935—Protamine Insulin	Hagedorn
1925	<i>Parathormone</i>	Collip
	A T 10	
1928	<i>Chorionic gonadotropins</i>	Aschheim and Zondek
1929	<i>Crystalline estrone</i>	Doisy
	1938—Stilbestrol	Dodds
1932	<i>Androsterone</i>	Butenandt
1934	<i>Progesterone</i>	Slotta, etc.
1936	<i>Desoxycorticosterone</i>	Reichstein

The endocrine extracts, as well as the pure crystalline products employed in therapy, may produce clear-cut effects. Nevertheless, this need not signify that they represent the hormones exactly as they exist and act within the living organism where they most probably are linked to large protein molecules. This is well illustrated by the thyroid hor-

\*Address at a meeting of the Mount Sinai Hospital, November 24, 1943.

mone to which I shall refer presently. Another example is at hand in epinephrine, a comparatively simple chemical entity which exerts a multitude of pharmacologic actions. I always have considered it a *partial* hormone, a fragment let us say, forcibly torn from a larger and more complex body which in nature exerts functions different and more subtle than those of the drug we use in medicine.

*Thyroid.*—I have already mentioned the use by Murray of desiccated thyroid substance. This same drug still is widely employed, mainly in the treatment of thyroid deficiency of which cretinism and myxedema are the best examples. It also is applied in the treatment of obesity as an adjuvant to a reducing diet. It has proved effective in the relief of retardations of growth and development in childhood and adolescence, as well as in all conditions accompanied by reduction of the basal metabolism, no matter what their origin, because of its calorogenic action which causes the cells to metabolize at a higher rate and accelerates the combustion of all the foodstuffs. It should not be employed, or only with great caution, in states of malnutrition.



Thyroxin

Fig. 1.

In 1914, Kendall isolated a pure chemical entity known as thyroxin (a tyrosene compound). This substance exhibits the same therapeutic properties as the gland desiccate. A closely related compound, also obtained from the gland, is diiodotyrosin, which, pharmacologically, is almost inactive. The modern concept may be formulated somewhat as follows. The thyroid produces thyroxin and diiodotyrosin in combination with a large protein group (globulin) to form a molecule of 675,000 molecular weight. Our crude concentration and extraction methods tear off fragments, of which one, thyroxin, retains pharmacologic activity. I have found no advantages over thyroid extract, attributable to the use of thyroxin. More recently an active substance of increased potency has been prepared by iodination of protein of nonthyroid origin (Reinecke and Turner).

In prescribing thyroid extract, it is well to remember that children and adolescents show marked tolerance to the drug and may require disproportionately high dosage. On the other hand, after forty, particularly in the presence of cardiovascular and renal diseases, undue sensitivity and atypical response may be anticipated and should be guarded against. Other less common uses of thyroid extract will be mentioned later.

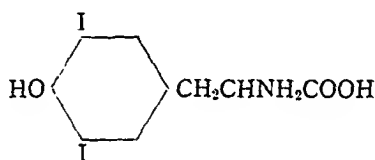
In this connection the palliative use of iodine in hyperthyroidism and in the mass treatment for the prevention of endemic goiter (Marine, 1921) deserve at least mention. The recently advocated treatment of hyperthyroidism, by means of thio-uracil, does not fall within the frame of my discussion.

*Posterior Pituitary.*—In 1895 Sharpey-Schafer discovered "pituitrin." Not until 1928 was the extract sufficiently purified to permit

Kamm to separate it into two fractions, oxytocin and vasopressin (pitressin). Oxytocin acts upon the uterine musculature; vasopressin contracts the peripheral blood vessels, stimulates intestinal peristalsis and also contains the antidiuretic factor.

For the past forty years, pituitrin and, for the last fifteen years, its two factors (oxytocin and pitressin) have proved useful pharmaceutical agents. Obstetricians initiate labor at term by injecting repeated, graduated doses either subcutaneously or intravenously; control postpartum bleeding at cesarean section, after labor or abortion. Surgeons employ it to stimulate the sluggish or parietic intestine postoperatively. It is a powerful drug which must be used with caution. Dystocia, employed in its broadest meaning, definitely contraindicates the use of pitressin, because uterine or intestinal rupture may result if an obstruction exists.

Posterior lobe extracts have a more strictly endocrine application in controlling the excessive diuresis of diabetes insipidus. Here the extract acts in a substitutional role, replacing the deficient antidiuretic factor. Not only subcutaneous but also sublingual and intranasal application proves effective. Pitressin tannate, by subcutaneous injection, is said to have a more prolonged action.



Diiodotyrosine  
Thyroglobulin Molecular Wt. 675000

Fig. 2.

Intermedin, a product of the intermediate pituitary lobe which is well marked in some species (first described by Zondek in 1932), has shown in my hands, no superiority to the other posterior extracts in the treatment of diabetes insipidus.

*Adrenal Medulla: Epinephrine.*—The first chemical identification of any hormone was achieved almost simultaneously and independently by Aldrich and Takamine in 1901. Epinephrine or adrenalin proved a popular drug in temporarily elevating the blood pressure in collapse. It soon became apparent that continued intravenous administration proves dangerous because of the sudden and permanent depression of blood pressure which supervenes. Epinephrine shows a paradoxical reaction on the bronchial musculature, relaxing spasm and therefore proving useful in the relief of asthma. In hay fever and obstructive coryza, epinephrine sprays shrink the engorged turbinates. Because of its local vasoconstricting action, today the main use is to prolong local anesthesia by confining the anesthetic to circumscribed areas.

In passing I might say that this is neither the place nor have I the courage to enter into the still hotly debated field raging about the physiologic properties of epinephrine which include its widely varied effect upon the various unstriated muscle groups, its role in maintaining tonus, its manifold influences upon the autonomic nerves and centers, as well as upon metabolism. Except for its local ischemic action, epinephrine has been superseded largely by other new synthetic drugs (Fig. 3).

*Pancreas.*—Long anticipated, feverishly sought after, insulin finally was obtained in 1922, by the combined efforts of a surgeon and physiologist, Banting and Best. With its discovery, the huge and widespread group of diabetics found relief and safety. In 1935, Hagedorn introduced protamine insulin, a more prolonged-acting insulin. The control of diabetes has become a special branch of endocrinology upon which I shall not venture.

My experience with insulin in conditions of malnutrition and in the treatment of dysmenorrhea, for which it was recommended, has been disappointing. Insulin likewise is employed in the production of hypoglycemic shock in the treatment of schizophrenia.

*Parathyroid.*—Three years after the discovery of insulin in 1925 Collip, who had contributed greatly to making insulin clinically available by eliminating its protein contaminant, announced a parathyroid extract with which he controlled the toxic phenomena occurring after parathyroid deprivation. The extract is crude and rapidly produces an increasing resistance or immunity which the discoverer ascribes to an "antihormone" action. Parathormone is of value during the critical

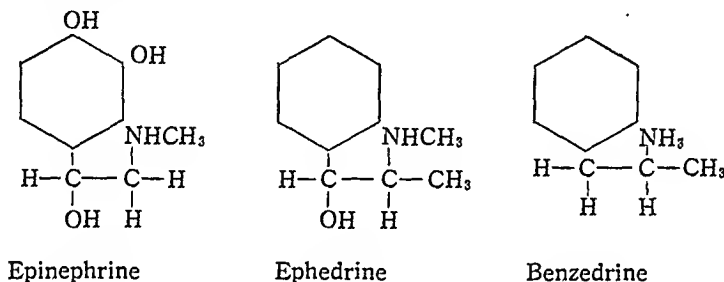


Fig. 3.

postoperative days following a partial removal of parathyroid tissue, either accidental or designed. In the acute stage it controls tetany and averts death. In chronic parathyroid deficiency, the rapidly increasing resistance to the drug necessitates the simultaneous exhibition of dihydrotachysterol, a reduction product obtained from irradiated ergosterol, known also as A T 10. However, A T 10 alone was unable to keep the one patient whom I was privileged to watch for many years, in complete calcium equilibrium even when huge doses of vitamin D were given simultaneously. The combination of parathormone in small doses with A T 10 kept her in perfect health.

According to Silbert, some relief, and in early cases, partial arrest, may be obtained in scleroderma by the continuous, cautious exhibition of A T 10. As the drug increases the blood level of calcium, excessive elevation must be watched for and guarded against.

*Anterior Pituitary and Related Substances.*—The gonadotrops include extracts of the prepituitary gland or adenohypophysis, concentrates of the blood serum of pregnant mares, and the chorionic gonadotropins, derived from pregnancy urine. None of these have been purified; their chemical structure is unknown.

Through the pioneer work of Philip E. Smith and simultaneously that of Bernard Zondek in 1927, the stimulating and regulating action of the anterior pituitary gland upon the gonads—both ovaries and testes—was discovered. Since then many other properties of the hypophysis have been demonstrated but these do not as yet warrant general clinical

application. I refer to the lactogenic, thyrotropic, adrenotropic, growth stimulating, ketogenic, and other factors which may be clearly demonstrated in the laboratory.

Up to the present, none of the prodncts obtained from the anterior lobe itself deserve clinical consideration. I state this categorically despite the glowing reports found in the literature; I base my opinion upon extensive and controlled trial and observation.

The serum of pregnant mares obtained a transient popularity in the treatment of sterility. It was injected intravenously in order to produce ovulation. Today a much more cautious attitude is observed. Personally, in a well-controlled clinical experiment, I have never been able to demonstrate that it produced ovulation in women.

The chorionic gonadotropins obtained from the urine of pregnancy are useful in initiating the descent of cryptorchid testes, particularly in the age group of six to twelve years. Approximately twenty-five per cent of the patients respond by permanent descent of the testes into the scrotum. I give 100 units intramuscularly three times weekly for from seven to eight weeks. If there is no result, it is well to wait six months in order to permit the refractory phase to diminish and then give 1,200 units subcutaneously at one injection. This large dose, even if unsuccessful, will cause localized pain at the site of the hidden gonad and thus guide the surgeon in planning his operation. Today it is almost obligatory to precede operation for undescended testicle by adequate gonadotropic therapy.

The control and even cure of menorrhagia and metrorrhagia by means of chorionic gonadotropins were accepted almost without dissent a few years ago. Today all careful observers agree that this hope was illusory. This affords a striking example of the *post hoc* and *propter hoc* attitude which has so frequently misled in endocrinology, and which is due to loose thinking, lack of critique, and inability or unwillingness to differentiate between success due to coincidence or to therapy. The same disillusion applies to many other uses recommended for gonadotropins.

*The Steroid Hormones.*—The chemical structure of the steroid hormones was rapidly clarified by the work of many biological chemists. The foundation for this stupendous advance was based upon the observation of S. Loewe and Lange in 1926, that the urine contained estrogenic substances. From this readily obtainable and water-soluble source, free from many contaminants of similar solubility to that of the steroid hormones contained in the tissues, Doisy, in 1930, crystallized a pure estrogen. In rapid succession investigators determined the structure of the estrogens, androgens, progestins and adrenocortical hormones. They all were found to belong to the general group of cyclopentenophenanthrenes, a group closely related to the universally distributed cholesterol.

How useful to the clinician have these new, potent hormones proved? It is well to bear in mind that all the steroid hormones, not only react upon their end organs or, the term of today, their "target" glands, but also affect the anterior pituitary by diminishing its output of stimulating or excitatory factors. Therefore exhibition of a sufficient quantity of estrogen, for example, to a menstruating woman, will disturb the rhythm of her cycle because it depresses the production of the stimulating gonadotropic hormone of the prepituitary though it directly stimulates the uterine tubular tract. Given to an amenorrheic female, it similarly depresses the anterior pituitary action, and therefore must depress follicle growth simultaneously, thus defeating the very purpose for which the



clinician prescribes the drug. Analogous depression of hypophyseal action results when progestin, androgens or adrenocortical hormones are given, the depression being very specific upon the various hypophyseal factors.

*Estrogens.*—A number of natural estrogens are available. Of these, estradiol and its benzoic ester are the most powerful. Estrone is next in strength. Estriol is the weakest. In addition, we now have a cheap synthetic estrogen, diethylstilbestrol (commonly called stilbestrol) as well as hexestrol (Fig. 5). The action of both natural and synthetic estrogens is identical.

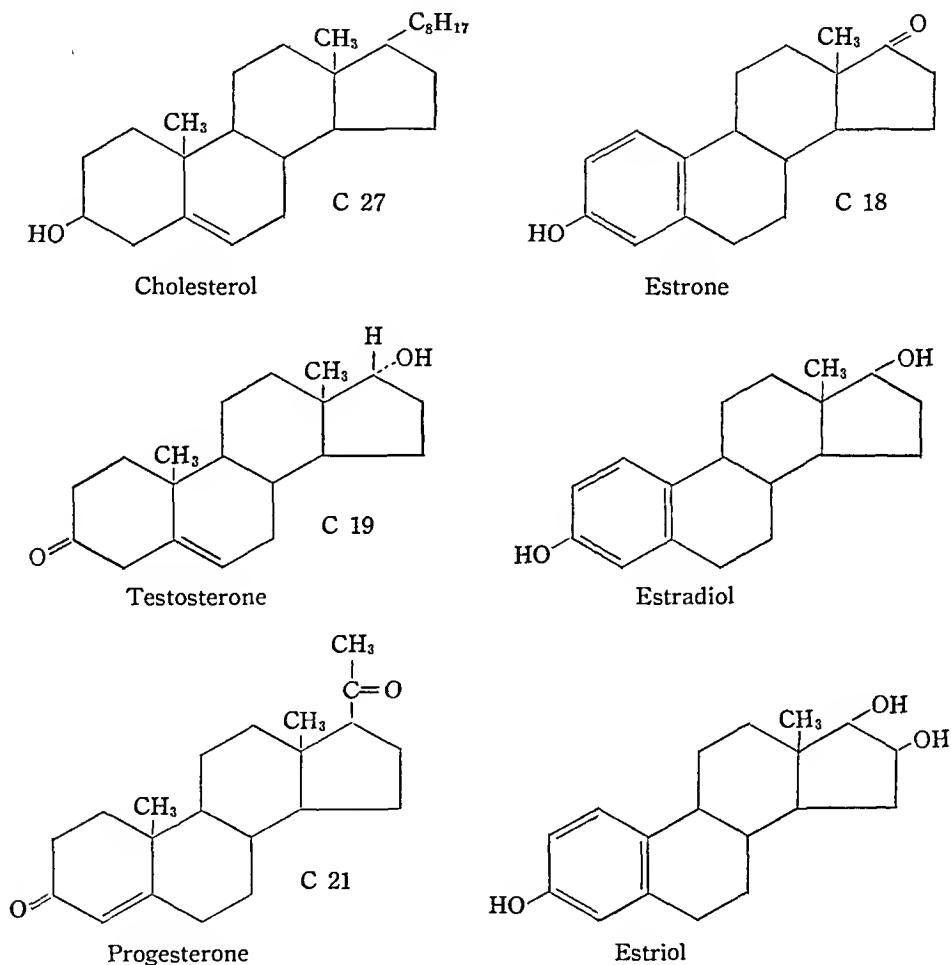


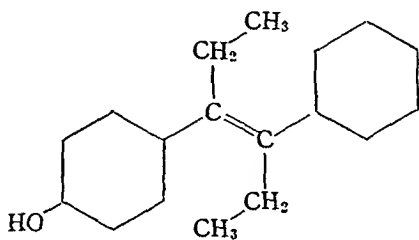
Fig. 4.—Structural formulas of cholesterol and steroid hormones. All have in common the cyclopentenophenanthrene nucleus.

After many years of wild and often senseless clinical application, the indications for the employment of estrogens have contracted to the following, first and foremost, the relief of the neurovascular, arthritic and nervous symptoms of the menopause. Estrogens are contraindicated in the preclimacterium, even if menstruation is no longer regular and flushes are complained of. If given at this time, excessive and more irregular bleeding may be anticipated, and indefinite prolongation of the climacteric condition may be induced, extending over many years. I have seen women of seventy, who still required or believed that they re-

quired estrogenic therapy. The giving of estrogens during the *preclimacterium* is one of the commonest errors of which both specialists and general practitioners are guilty. I see many patients who, as a result of this mistaken treatment, exhibit bizarre mixtures of menorrhagia, metrorrhagia, leucorrhea, painful and lumpy breasts, etc.

Estrogens, preferably in the form of vaginal suppositories, exhibited over ten to fourteen days, relieve the occasional and repeated attacks of senile vaginitis and dysuria which may develop years after the menopause has set in.

Estrogens, likewise, have proved useful in thickening and keratonizing the infantile and adolescent vulva and vagina and thus shortening the course of gonorrheal vulvovaginitis. Today this mode of therapy has been largely superseded by the quick action of sulfadiazine in curing gonorrhea.



Stilbestrol

Fig. 5.—The strong synthetic estrogen "stilbestrol" as depicted by Dodds.

Suppression of lactation may be effected by large doses of estrogens immediately post partum (5 mg. stilbestrol daily).

Recently a new and astounding effect exerted by the estrogens has been discovered. In adequate dosage, 5 mg. of stilbestrol daily, relieve the pain and may produce at least temporary regression of bone metastases due to carcinoma of the prostate. This antimaseulinizing effect of estrogens has encouraged investigation of the effect of large doses of androgens for the relief of inoperable breast cancer in the female. Preliminary reports indicate that stimulation instead of regression occurs.

I have never been able to cure or even greatly palliate the symptoms of kraurosis vulvae, mainly a menopausal disease, nor obtained real or permanent relief of pruritus vulvae by means of estrogens. I shall not dignify by referring to them, the many and illogical other applications of estrogens which have been recommended.

For the treatment of the menopause symptoms, I recommend one mg. of stilbestrol by mouth, immediately before retiring. If taken with a small amount of food, the symptom of nausea rarely appears. Should nausea persist, we are forced to resort to estradiol tablets of which  $\frac{1}{2}$  mg., three times a day suffice. This drug is very expensive in comparison to the cheap synthetic estrogen. I have not given estrogens by hypodermic injections for many years. In the few patients who have claimed that oral treatment was ineffective, I have convinced myself by means of hormonal studies which show the disappearance of excessive gonadotropic factor from the urine, as well as by vaginal smears which become positive in response to the therapy, that the full drug effect was attained, and that the continuance of the symptoms might justly be ascribed to

profound psychic convictions due to the tales current among the patient's friends or to the injudicious remarks of the physician.

The introduction, subcutaneously of pellets, consisting of crystalline estrogen, is practicable but rarely indicated.

*Progestins.*—The corpus luteum hormone now is produced commercially by synthesis of steroids. This has somewhat reduced its cost. Progesterone is available for hypodermic use; pregnenolone for exhibition by mouth.

There are no reliable criteria for judging the effectiveness of this therapy in the human being. Endometrial biopsy is rarely convincing, particularly as the secretory phase has been shown to occur, at least in the monkey, in response to estrogens alone, although usually we ascribe the secretory phase to progestational, that is to corpus luteum action. Clinically, while I still employ both forms of the drug in the treatment of threatened abortion, in the prophylaxis of habitual abortion, and less often for the relief of dysmenorrhea, I am far from convinced of its efficacy. I emphasize this because the results are variable and inconclusive. They do not lend themselves to analysis. If employed, the dosage should be high, 10 mg. progesterone daily, or at least 40 to 80 mg. of pregnenolone.

In a recent case of universal alopecia in the female, prolonged subcutaneous injections of progesterone have been followed by a profuse regrowth of the head hair as well as of partial return of the eyebrows and cilia, without appearance of any labial hair growth.

*Androgens.*—Trial as well as a return to common sense has served to contract the field for application of androgenic therapy to within fairly well-defined limits. Available are oily solutions of testosterone propionate for injection, and tablets of methyl testosterone for oral use. Eunuchs, eunuchoids, and persistently infantile males who have passed the age of eighteen years are handicapped in their activities, in their ability to obtain employment, and in other spheres because of their beardlessness, high-pitched voices and asexual configurations. Some, at least temporary, relief of these deficiencies can be obtained by injecting up to 1,000 mg. of testosterone propionate during the course of seven to eight weeks, using a 50 mg. dose three times a week. Usually these patients develop some growth of beard, their voices deepen, redistribution of fat occurs, and a transient stimulation of libido supervenes. In consequence of this improvement, at least their self-assurance and self-respect increase.

Androgen therapy should not be employed either in retardation of growth, or in undescended testicles, as well as in males with Fröhlich's syndrome until their growth period has definitely been passed because of the regressive action of androgens exerted upon the testes. I might mention that huge doses of both estrogens and androgens fail to arrest growth in the gigantism of adolescence.

A temporary rejuvenation by androgenic therapy may result in aging males who have become listless, neurasthenic, particularly about their loss of libido, and who show a general let down, negligence, and weakness of memory. The effect, however, is so temporary that this therapy should be limited to very few and selected patients. Symptoms described as the "male climacteric," neurovascular and psychic, are uncommon. If actually present, they are transiently relieved by androgenic therapy.

Androgens are ineffective in the treatment of azospermia. I have convinced myself of this by prolonged control of semen specimens. The treatment of prostatic hypertrophy by means of androgens has been discontinued.

The antifeminizing power of androgens has been utilized in gynecology to relieve the excessive flow of menorrhagia and metrorrhagia, as well as to control the pain of dysmenorrhea. The effects can be obtained. They are temporary and purely palliative. Moreover, the dosage required approaches the threshold dose which produces masculinization so closely that in some instances permanent enlargement of the clitoris, hoarsening of the voice and hirsutism cannot be avoided. I therefore advise against this type of therapy.

*Adrenal Cortical Extracts.*—The last of the steroid hormones requiring consideration is adrenocorticosterone.

In Addison's disease, a patient may be maintained in good health for many years by the judicious use of adrenocorticosterone or/and adrenal cortical extract. The commercial extracts have proved entirely unsatisfactory. In some patients who respond gratifyingly over long periods of time to the crystalline hormone, occasional crises may arise, in which the intravenous use of an active extract, obtainable only from a few experimental laboratories, may be required for varying periods of time. Just as in diabetes, dietary supervision is obligatory. A low potassium, high sodium diet, bolstered by the giving of 15 grams of sodium chloride or sodium citrate additionally, is indicated. The supervision of this group, fortunately small in number when compared with diabetics, necessitates frequent and accurate laboratory control. Of these, electrolyte equilibrium and nitrogen balance determinations are essential. Therefore such patients should be entrusted to the care of physicians especially equipped for such studies. I have noted that premenstrually or during the menses, some women, suffering from Addison's disease, may temporarily require larger doses of hormone.

The implantation of pellets consisting of crystalline adrenocorticosterone involves the risk of sudden uncontrollable peaks of absorption, with consequent symptoms of acute hyperadrenalism, which may prove fatal to the already debilitated patient.

If a patient is to be subjected to operation for hyperadrenalism due to hyperplasia, adenoma or carcinoma of the cortex, she will require careful preoperative study, preoperative treatment, and especially the most meticulous postoperative supervision. In conditions of adenoma or carcinoma, the unaffected adrenal almost always has undergone "compensatory atrophy" if this descriptive misnomer can be used. The frightful postoperative mortality of adrenalectomy may be reduced if surgeons will call in the assistance of a medical man trained in this very special field or learn to employ the proper precautions themselves.

### Discussion

At the outset, I should have warned that of necessity my presentation would prove both eclectic and didactic. By now it will have been realized that unless specially emphasized, as in the tentative use of progesterone, I have limited my recommendations to fully authenticated and proved application of endocrine substances. To forestall many anticipated queries, covering particularly the field of functional conditions in the female, the treatment of which has harassed the entire medical profession

for years, I shall conclude my remarks by briefly touching upon the treatment of several of these syndromes. Let me warn once more, as I have done on many previous occasions, that a condition should not be diagnosed as "functional" unless sufficient evidence warrants such a conclusion. Such care will prevent some of the ludicrous errors I have encountered. I instance the giving of estrogens to girls with absent vagina in order to "cure" their persistent amenorrhea. Equally embarrassing to the physician was the persistent prescribing of thyroid for amenorrhea to a "virgin," whom he had known since infancy, up to her seventh month of pregnancy. I have seen repeatedly chorionic gonadotropin (which, by the way I repeat is ineffective) prescribed to control vaginal bleeding due to a tubal pregnancy.

*Amenorrhea.*—Unless resulting from remedial constitutional causes, such as obesity, hypothyroidism or malnutrition, amenorrhea does not respond to direct endocrine treatment. If a woman has a uterus, whether ovaries are present or not, she can be made to bleed. In amenorrhea, if 500,000 to 1,000,000 international units of estrogens have been given in the course of fifteen to thirty days, withdrawal bleeding will result, within five to ten days. Such treatments are valueless. A dose of only 30,000 international units given to a woman of seventy years will produce the same effect. This clinical experiment shows that in amenorrhea the threshold of response bleeding to estrogens is elevated. The cause of this elevation is unknown.

*Menorrhagia and metrorrhagia* can be of functional origin. Neither the gonadotropins, progesterone, nor estrogens are effective. Large doses of androgen temporarily arrest the bleeding but entail the risk previously referred to.

There is a small group suffering from puberty bleeding, adolescents whose basal metabolism falls to the minus twenty or lower levels. These girls respond promptly to thyroid medication and relapse if this treatment is stopped. This response appears paradoxical, for another hypothyroid group, more numerous than the preceding, suffering from amenorrhea, bleeds cyclically in response to the same medication. These two groups fully illustrate how little we as yet understand the mechanism of menstruation.

Consequently I resort more frequently today than previously to such nonendocrine remedies as ergot and curettage in younger patients, to x-ray and radium in older women, to relieve persistent and excessive bleeding.

*Dysmenorrhea.*—Dysmenorrhea remains a thorn in the side of both the general practitioner and gynecologist. These patients continue to wander from physician to physician, receive transient relief from any therapy and then soon relapse. Yet the majority of sufferers fundamentally are not neurasthenics although they may become so. Constitutionally, many are handicapped by infantilistic stigmas. The majority have a low threshold to pain. Some "outgrow" the condition, to use an old and homely phrase. Others are relieved by marriage, many more by parturition. A few reach the thirties unrelieved. Pregneninolone in doses of 20 to 40 mg., up to 80 mg. during a height of paroxysm, relieves some patients for a time. Estrogens give no relief. Our efforts must be to keep these patients from resorting to morphine. Codeine and atropine, to the point of tolerance, and coal tars remain our stand-by in the majority, and often insure relief. Dilatation under anesthesia and

the stem pessary give but temporary relief. The problem, though pressing, as yet remains unsolved. In the older group, x-ray castration should be resorted to.

In summary, I may state that in the majority of instances, where there is a deficiency of a given hormone, substitutional therapy proves effective. It is to be regretted that the vital function of the prepituitary can as yet not be replaced. The commonest error is that of employing hormones when no deficiency exists.

Overaction of the glands of internal secretion can be reduced by surgical means, adenoma of the thyroid, pancreas, pituitary and adrenal cortex may be instanced. Another method available is the use of x-ray therapy. Neither of these methods is ideal. As early as 1916, Hermann pointed out the antimasculinizing effect of estrogens. The interregulation and counteracting influences of the various glands upon each other were recognized by Eppinger, Falta and Rudinger in 1908, but only recently have attempts to utilize these actions been applied to clinical investigation. It is toward this goal that future research should be directed.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Gynecologic Operations

**Adams, William M.:** Construction of an Artificial Vagina, Surg., Gynec. and Obst. 76: 746, 1943.

The author reports two successful cases of construction of artificial vagina, using a one-half thickness skin graft over a mold. He has introduced three innovations which are worthy. These consist of the use of three different types of molds. The first is made of sponge rubber, over which is placed a wire frame. The graft is glued to this with rubber cement. This is removed at the end of 10 days and replaced by a perforated plastic mold. The latter is worn for one week and replaced by a condom-covered rubber sponge, this being used off and on until no danger of contraction remains.

LT. L. M. HELLMAN, M.C., U.S.N.R.

**Koller, T.:** Therapeutic Pelvic Puncture in Gynecologic Disturbances, Schweiz. med. Wchnschr. 73: 374-377, 1943.

According to the author the therapeutic indications for the use of pelvic puncture are as follows: (1) Chronic inflammatory adnexal masses where prolonged conservative treatment fails to bring about improvement, and where operation is dangerous because of the risk of peritonitis. In these cases a pelvic puncture should not be done unless a more or less fluctuating mass is felt between the uterus and rectum. Recently in such cases, the author has instilled a sulfonamid preparation after emptying the abscess cavity; (2) Adnexal tumors with pelvic peritonitis and rapid exudation; (3) To differentiate between extrauterine pregnancy and chronic adnexal inflammation. In all of these cases there is no danger of infection from the procedure because infection is already present. The author warns against the use of pelvic puncture to empty follicle and corpus luteum cysts. In such cases it is safer to perform laparotomy. In rare cases, however, it is permissible to puncture an ovarian cyst through the vagina as for example in a woman so critically ill, that laparotomy is contraindicated.

The author has never observed any complications from pelvic puncture. In cases where pus is encountered, it is drained and nothing further is done. Where, however, blood, serous fluid or the contents of a dermoid cyst are obtained, an immediate laparotomy is done.

J. P. GREENHILL

### Newborn Infant

**MacGregor, Agnes R.:** The Causes of Fetal and Neonatal Death, Edinburgh M. J. 50: 332, 1943.

The continuing high infant mortality rate of Scotland is rightly regarded as a national reproach to the medical profession of that country. So reports the author

who has made the determination of causes of these increased infant mortality rates a subject of special study at the Simpson Memorial Maternity Pavilion.

In a three-year period, 1939 to 1941, at the above institution, there were 7,523 live births, with 342 neonatal deaths, and 603 stillbirths, making in all 945 deaths. Of these, 338 liveborn and 422 deadborn children were examined post mortem, making 760 autopsies. The four principal causes of death for both groups include: (1) developmental malformations (142 cases) 18.7 per cent, (2) intracranial hemorrhage (277 cases) 36.4 per cent, (3) asphyxia (306 cases) 40.3 per cent and (4) infections (156 cases) 20.5 per cent.

The neonatal mortality rate per 1,000 live births was 45.5 for all infants (7,523 cases), 19.0 for full-term infants (6,815 cases) and 299.0 (708 cases) for premature infants. Expressed in another way these figures show that 9.4 per cent of all live births were premature which group contributed 62 per cent of the deaths, while the 90.6 per cent that were full-term births accounted for 38 per cent of the deaths.

The author has omitted from her list of causes of fetal and infant death such vague connotations as prematurity, atelectasis and thymic death. The writer reasons most logically that it is the development of pathological conditions that eventuate into fetal or infant death which must be considered rather than these so-called "half-diagnoses" which at most are but secondary contributing factors.

The writer concludes her article with a concise analysis of her findings encountered in each four main etiologic categories of fetal and neonatal death. She emphasizes, under infections, the frequently overlooked but peculiar susceptibility of the newborn infant to infection by common organisms of supposedly low virulence, e.g., the organisms of the *B. coli* group, in the first month, and especially in the first three weeks are often the cause of pneumonia and the most common cause of meningitis. Yet after the first month the *B. coli* group are virtually never found in either role.

CLAIR E. FOLSOME

**Guzman, V. G.: Intracranial Hemorrhage in the Newborn Infant, Obstet. y ginec. Latino-Americanas 1: 132-153, 1943.**

At the San Borja Maternity, Chile, intracranial hemorrhage accounted for 15.6 per cent of the newborn deaths over a period of eight years. Since 1939 there has been a decline in the number of newborn babies who showed signs of intracranial hemorrhage but who did not die. This is due to improved treatment of syphilis, better prenatal care and more careful conduct of labor, whereby unnecessary interference was avoided. During the last two years, vitamin K has been used prophylactically. The importance of congenital weakness and vascular fragility is supported by the fact that half of the babies who had cerebral hemorrhage weighed less than 2,500 grams. Responsibility for the intracranial hemorrhage can be attributed to the obstetrician in only 40 per cent of the cases. In the author's series intracranial hemorrhage was observed in 17.5 per cent of the babies delivered by the breech, in 10.7 per cent delivered by forceps and in 10 per cent delivered by internal version. The death rate of babies with cerebral hemorrhage is 77.4 per cent. Of the remaining 22.6 per cent some show evidences of injury to the nervous system late in life. There is no curative treatment for this complication hence prophylaxis is of the utmost importance.

J. P. GREENHILL

**Gavioli, Richardo L.: Fetal Ichthyosis, Arch. Clin. obst. y ginec. "Elisco Can-tón" 2: 134-142, 1943.**

The author reports a case with a study of the pathology. A premature female fetus, 35 cm. long, weighing 1,050 grams, displayed the characteristic signs of severe



ichthyosis; the hard skin, broken by deep lesions; the large immobile mouth, transversely oval; severe conjunctival inflammation which closed the eyes; atrophy of the fingers, nails, etc., and of the hands and feet and ears. The fetus survived 40 hours. Histologic study, as in other reported cases, revealed the typical lesions of epidermal hyperkeratosis and discrete lesions of dermal keratosis and fibrosis. The etiologic factor in this case may have been the consanguinity of the parents, who were first cousins.

J. P. GREENHILL

Leon, Juan: Fetal Gigantism, *Bol. soc. de obst. y ginec.* 21: 781-792, 1943.

The author reports a study by Alberto S. Coatz made in the Eliseo Cantón Clinic. Any fetus born weighing 5,000 or more grams was included in this classification. In 51,000 births, there were 125 cases of fetal gigantism (0.24 per cent), i.e., one in every 400 births. The maximum weight was 6,500 grams. Of the 125 cases, 54 of the mothers were Argentinians; the others foreigners. The age of the mother is not a factor in the etiology of fetal gigantism. Large infants seldom are born of primiparas; in this series 93 per cent of the mothers were multiparas, the majority secundiparas. There was no relation between fetal gigantism and the interval since the last pregnancy. The duration of menstruation was not an etiologic factor. Heredity undoubtedly plays a role in this type of case. Prolongation of gestation has an insignificant influence in production of large infants.

Excess eating by the mother can affect the infant, but this is not equal for all fetuses; hence individual factors must enter in, possibly dependent on fetal metabolism. The sex of the fetus has an important role, for twice as many male as female fetuses are gigantic. Hormonal influences, though not well understood, and fetal metabolism undoubtedly are important. Little value is attributed to the seasonal factor in the etiology.

Diabetes and syphilis are of but slight importance; in the 125 cases there was only one diabetic mother and three were syphilitic.

Current diagnostic methods, inspection and palpation, suffice to make a diagnosis of fetal gigantism. Simple radiography may clarify a doubtful diagnosis. A characteristic finding is fetal hyperflexion, necessitated by lack of space in the uterus.

Cephalic presentation is most common in these cases (91 per cent). Breech presentation occurred in 5.4 per cent and transverse in 3.5 per cent. Labor is prolonged in cases of fetal gigantism, particularly in multiparas. Spontaneous parturition occurred in 55 per cent of the primiparas and in 44 per cent of the multiparas. Operative interference was necessary in the remaining cases. From this it is concluded that fetal gigantism represents a serious complication in childbirth.

The puerperium was normal in 83 per cent; subfebrile in 10 per cent; febrile in 7 per cent. The maternal prognosis is serious but not dangerous. It is affected by the number of previous deliveries, dimensions of the fetal diameters, type of presentation, etc. The maternal mortality in this series was 2.4 per cent. The fetal prognosis is bad. The mortality in this series was 28 per cent and the fetal morbidity was extraordinary.

Prophylactic treatment consists in induced premature delivery. Cesarean section should be done in selected cases. At the time of delivery, the problem must be solved according to the type of dystocia. In cases of failure, embryotomy must be done.

J. P. GREENHILL.

## Complications of Pregnancy

Harmon, Paul F., and Hoyne, Archibald: Poliomylitis and Pregnancy, J. A. M. A. 123: 185, 1943.

The authors report two cases of acute anterior poliomyelitis complicating pregnancy with fetal death occurring in one of the two cases, explained by the author as being due to fetal asphyxia as a result of a bulbar poliomyelitis. In order for infection to occur in the fetus, one would have to assume a blood stream infection passing through the placental barrier. There is no evidence that the virus of poliomyelitis is present in the blood stream with any degree of regularity if at all, and if it were, it would still have to be assumed that some irritant process was at work in the central nervous system of the fetus in order for infection to occur.

The conclusion of Kleinberg and Horwitz is quoted, "that pregnancy complicating acute anterior poliomyelitis may be anticipated to progress normally with a normal termination of labor and with a normal offspring." These latter authors found no evidence of intrauterine acute anterior poliomyelitis in 29 cases reported by them. They also concluded that there is no indication for interruption of pregnancy at any stage except for those reasons that would be operative in nonparalytic females. The passive immunity derived by the offspring from the mother does not persist for long, since a number of cases of acute anterior poliomyelitis under the age of one month have been reported.

WILLIAM BERMAN.

Kapeller-Adler, R., and Cartwright, J. A. Vitamin B<sub>1</sub> and Toxemia of Pregnancy, Edinburgh M. J. 50: 305, 1943.

The authors, concerned with previous reports in medical literature suggesting a relationship between vitamin B<sub>1</sub> deficiency and toxemia of pregnancy, determined to investigate the possibility of this purported etiological correlation.

Nineteen patients with mild or severe pre-eclamptic toxemia were treated with vitamin B<sub>1</sub>. The vitamin B<sub>1</sub> ("Benerva Roche" and "Berin") was administered both orally and intramuscularly. A normal course of treatment consisted of ten intramuscular injections of vitamin B<sub>1</sub>, 25 milligrams the first day and 10 milligrams on each of the succeeding nine days. In some instances the dosage was increased to 25 milligrams daily for the first four to five days. No beneficial effect was seen in any of these cases.

In the group of patients presenting severe pre-eclamptic toxemia the effect of vitamin B<sub>1</sub> treatment may even be described as detrimental. The authors contend that these results were to be expected taking into consideration the affinity of vitamin B<sub>1</sub> for histaminase. They conclude that the therapeutic use of vitamin B<sub>1</sub> in toxemia of pregnancy should be discouraged.

The authors substantiate their conclusions with careful biochemical analyses and close clinical observations which are well summarized in two tables and two graphic figures.

CLAIR E. FOLSOME.

Davidson, L. S. P., Davis, L. J., and Innes, J.: Studies in Refractory Anemia. III., Edinburgh M. J. 50: 431, 1943.

The authors in this article, the third section of their studies in refractory anemia, discuss a topic of considerable importance to obstetricians—the refractory anemia with hypercellular and megaloblastic marrow occurring in pregnancy and the puerperium.

In a summary of ten cases, followed for two years, the authors report that in all ten instances the anemia was severe. The hemoglobin readings ranged from 17 to 52 per cent during pregnancy or the puerperium with megaloblastic sternal marrow pictures. All the cases displayed temporary refractory periods varying

from two weeks to four months in spite of intensive parenteral liver therapy supplemented by the administration of iron and vitamin concentrates. In the majority of the cases repeated blood transfusions were necessary for the maintenance of life during the refractory period. Eventually complete recovery occurred in all cases.

CLAIR E. FOLSOME.

Moscoso, Cesar Jacome: Eclampsia in the Quito Maternity, Bol. d. soc. de obst. y ginec. 21: 770-771, 1943.

The author reports a statistical study of about 50,000 pregnancies observed at the Quito Maternity since 1910. His figures show a lower incidence of eclampsia than in other reported series. In 22,567 pregnancies during the last five months (the period when eclampsia develops) there were 80 cases of eclampsia, an incidence of  $\sqrt{3.54}$  per 1,000. There was no indication that climate had any effect on development of eclampsia. In the dry season (5 months) there were 38 cases and in the damp season (7 months) 42 cases. Of the 80 cases of eclampsia, 47 were in primiparas (58.25 per cent); 11 in secundiparas; and 20 cases in later pregnancies.

The eclampsia occurred during pregnancy in 51 cases, during labor in 17 cases, and during the post-partum period in 12. Eight of the latter occurred within the first 24 hours after delivery, and in the others after 2, 3, 8 and 15 days.

In the 80 cases of eclampsia there were 29 maternal deaths (36 per cent). No reference to fetal mortality was noted in 9 cases; in the remaining 71, 30 died either before or after delivery (42 per cent).

In this series of cases both medical and surgical treatment was employed. Moscoso comments that since the mortality is higher than in most reported series, better methods of treatment must be found. He feels that improvement can be accomplished only by attention to the social factors and by educational measures. Many of the patients had not been seen prior to the development of severe eclampsia and had had no prenatal care.

The method of evacuating the uterus depends on individual circumstances and the condition of the patient. Other measures recommended include absolute quiet and avoidance of excitement; suppression of the eclamptic attacks by administration of morphine-chloral; maintenance of circulatory function; and bleeding to bring down arterial pressure. The last is contraindicated in the presence of anemia or imminent delivery.

J. P. GREENHILL.

Caso, Rogelio and Baez, Juan Jose: Pregnancy, Parturition and Puerperium in Nephrectomized Patients, Bol. d. soc. de obst. y ginec. 21: 816-820, 1943.

The authors report six cases. Four of the patients had nephrectomy for tuberculosis, one for pyonephrosis and one for lithiasis. In four women the pregnancy developed normally and was carried to term, with delivery of live fetuses. Three women had spontaneous deliveries and one required surgical intervention because of dystocia. In the other case, there was abortion of a dead, retained fetus. In one of the patients who ultimately had a spontaneous delivery, pyelitis developed during the second month of pregnancy. This was treated conservatively.

The authors conclude that three or four years should elapse after nephrectomy before pregnancy should be allowed, but this only if the remaining kidney is healthy. If the sole kidney is diseased, the pregnancy should be interrupted or sterilization should be carried out. The patient should have careful observation and study of renal function during the entire period of gestation. If there is any alteration in renal function which threatens the health of the patient, the pregnancy should be interrupted.

J. P. GREENHILL.

## Sterility, Fertility, Contraceptives

Müller, J. H. The Significance of Hysterosalpingography for the Diagnosis and Treatment of Sterility, *Schweiz. med. Wchnschr.* 73: 204-205, 1943.

In a group of 100 cases of sterility investigated by Müller, there were 64 cases of primary sterility and 36 cases of secondary infertility. In 46 per cent both tubes were patent, in 32 per cent both oviducts were closed and in 22 per cent only one tube was open. In a follow-up of 84 of the patients up to seven years, it was found that only 24 per cent of the patients became pregnant.

In 59 women no special therapy was carried out other than the hysterosalpingogram and 13 conceived. Hormone therapy was used in nine cases and three became pregnant. Ventrofixation was performed in 4 cases, tubal resections in 5, salpingostomies in 9, tubal implantation in 1, curettement in 5, and cervical dilatation in 2. Following these 25 operations only two women conceived; one after cervical dilatation and the other after unilateral adnexal resection and release of adhesions on the opposite side. This incidence of success following surgical operations, namely, less than 10 per cent agrees with the reports in the literature. The author believes that operation is justified in spite of the poor results because it will convince the patient that everything possible to overcome the sterility has been done.

J. P. GREENHILL.

Rabau, E., Halbrecht, I., and Casper, J.: Endometrial Tuberculosis as a Cause of Sterility, *J. A. M. A.* 122: 801, 1943.

The difficulty of the diagnosis of genital tuberculosis is stressed. There are very few clinical symptoms, and the diagnosis is usually accidental at either the time of operation or at the autopsy. A hypoplastic uterus is a frequent sign in genital tuberculosis. Methods for detection of genital tuberculosis that have appeared in the past literature are mentioned. The authors warn against salpingography as a means for diagnosing tuberculous salpingitis. They have used the endometrial biopsy method and they state that they have discovered a considerable number of cases of tuberculosis which had not given rise to any other sign or symptom. They found 20 cases of tuberculous endometritis in 208 endometrial biopsies studied for sterility. Tuberculous endometritis is quite compatible with patent tubes. The path of the infection of the uterine mucosa is uncertain. The authors feel that radical surgery should be reserved for only caseous processes.

WILLIAM BERMAN.

Hamilton, W. J., Barnes, Josephine, and Dodds, Gladys H.: Phases of Maturation-Fertilization and Early Development in Man, *J. Obst. & Gynaec. Brit. Emp.* 50: 241, 1943.

The authors present three early ova, one from a woman sterilized because of mitral stenosis; the second specimen from a woman sterilized because of a severe toxemia in her two previous pregnancies that resulted in miscarriages; and the third, from a woman who had a hysterectomy because of menorrhagia due to the associated presence of an ovarian cyst. From the history and the time of coitus, and the age of the specimen the authors conclude that ovulation occurs about  $14 \pm 1$  days before the beginning of the next period. There is some evidence from those few cases to show that the time of ovulation is more closely related to the beginning of the next menstruation than of the preceding one.

WILLIAM BERMAN.

Ramos, Alberto Peralta: Membranous Dysmenorrhea as a Factor in Sterility, *Obstet. y ginec. Latino-Americanas* 1: 117-131, 1943.

As emphasized by Alberto Peralta Ramos (Buenos Aires) membranous dysmenorrhea is important not only because it produces pain at the time of the menstrual flow but also because it causes sterility. Histologic study of the endometrium obtained in cases of membranous dysmenorrhea reveals that it is identical with that which is present during the last few days of the cycle except that it has not undergone autolysis. This is due to insufficient action of the physiologic, proteolytic and anticoagulating ferments.

The greatest pain in cases of membranous dysmenorrhea occurs just before and during menstruation when there is present the greatest amount of estrogen and the smallest amount of progesterone. The treatment recommended by the author is the use of gonadotropic hormones assisted by progesterone. In the future he intends to employ dehydrated plasma of pregnant women because this substance has yielded good results in some cases of menstrual irregularities.

J. P. GREENHILL.

Westman, A.: The Mechanism of the Transit of Ova in Women Observed During Laparotomy, *Schweiz. med. Wchnschr.* 73: 145-148, 1943.

Only a few operators have been fortunate enough to observe rhythmic contractions of the Fallopian tubes at the time of operation. However, as the author points out, with the Rubin apparatus tubal activity is, of course, registered on a kymograph. Mickulicz-Radecki studied the behavior of the tubes and ovaries in various phases of the menstrual cycle and found that at the time of ovulation the abdominal ends of the tubes came into intimate contact with the ovaries by means of activity of the tubes. Westman had previously shown that such a phenomenon takes place in many of the lower and higher mammals. This author also studied the mechanism of the transport of ova in women. At the time of operation he injected drops of lipiodol into the tunica albuginea and subsequently studied the position of the ovaries by roentgenography. He performed hysterosalpingography and thereby was able to study the relationship of the tubes to the ovaries. Serial roentgenograms showed that not only do the tubes possess motility but also the ovaries. The latter can move not only cranialward and caudalward but also on their long axis. This motility is brought about by contraction and relaxation of the smooth muscle in the ovarian ligaments and in the walls of the ovarian blood vessels. Roentgenograms showed that periodically the tubes bend around and encircle the ovaries. By means of this mechanism the expelled ovum is transported directly and quickly into the Fallopian tube.

J. P. GREENHILL.

Rochat, R. L.: Sterility of Ovarian Origin, *Schweiz. med. Wchnschr.* 73: 208-210, 1943.

According to the author the causes of sterility in the female may be divided into three groups: (1) Incapacity of the ovaries to produce ova or at least fertilizable ova; (2) Functional or chemical abnormalities in the genital tract which cause the death of spermatozoa or which prevent their union with ova; and, (3) Mechanical obstacles which prevent the union of sperm with ova. The second and third causes are easy to determine but the first is not. Likewise, whereas it is easy to detect abnormalities of spermatozoa by direct examination, this cannot be done with ova.

To determine the ovulatory function of the ovaries, two procedures are available namely, biopsy of the endometrium during the premenstrual phase, and a study of the temperature curve.

Ovarian dysfunction cannot be overcome by ovarian hormone therapy. But the author believes that a very satisfactory form of treatment is homotransplantation of an ovary. Such a transplant can act as a stimulant to a woman's defective ovaries and produce maturation of follicles. The author observed two pregnancies following homoplastic ovarian transplants in cases of hypofunction of the ovaries without apparent lesions.

A second form of treatment which may be satisfactory is the use of pituitary hormone. However, the urinary gonadotropins are not effective but the gonadotropic hormones derived from serum can produce maturation of follicles in women. At present since such gonadotropic hormones cannot be obtained, the author is resorting to blood of pregnant women because it contains a large amount of prolactin A and B.

J. P. GREENHILL.

Reist, A.: *The Therapeutic Significance of Tubal Patency Tests*, Schweiz. med. Wchnschr. 77: 206-208, 1943.

During the last 16 years Reist performed Rubin tests on 381 women and found the tubes closed in 127 or 33.5 per cent. Among the 254 women who had patent tubes, 75 or 29.5 per cent became pregnant. Of this group 69 women gave birth to living children, 4 had miscarriages and 2 had extrauterine pregnancies. In 13 per cent of the 254 cases, pregnancy immediately followed the tubal patency test. Hence the Rubin test is not only a diagnostic procedure but also a therapeutic one.

There is no unity of opinion concerning why the Rubin test leads to pregnancy in so many cases of sterility. The reasons advanced are: (1) The test produces an increased activity of the tubes; (2) Mild adhesions are broken down; and (3) Reist believes that the test in some cases produces an additional ovulation in the premenstrual period; (4) Rubin tests help ascent of spermatozoa.

The author is in favor of performing repeated tubal patency tests at intervals of 2 or 3 months. His maximum for one patient is 12 tests.

J. P. GREENHILL.

De Moraes, A., and Rosado J.: *Hysterosalpingography in the Diagnosis of Ectopic Pregnancy*, Obst. y ginec. Latino-Americanas 1: 19-32, 1943.

The authors employed hysterosalpingography in cases of ectopic pregnancy at the A. de Moraes Maternity Hospital (Rio de Janeiro). In all the cases operation confirmed the diagnosis. The authors emphasize that the injection of oil is unnecessary in the cases of ectopic gestation complicated by rupture and internal hemorrhage but this aid is of great value in doubtful cases. Hysterosalpingography is of greatest diagnostic value in the cases of unruptured tubal pregnancy. This method in the opinion of the authors is harmless and less dangerous than pelvic puncture, biopsy of the endometrium, pneumonocopy or pneumoroentgenography. The procedure is particularly useful in differentiating between a uterine angular pregnancy and an ectopic pregnancy.

J. P. GREENHILL.

Scherer, H.: *What Does Salpingography Accomplish in the Recognition of and Treatment of Female Sterility?* Schweiz. med. Wchnschr. 73: 147-149, 1943.

During the last 5 years the author employed salpingography in 80 cases of sterility. In this group there were 55 instances of primary sterility and 25 cases of secondary sterility. The causes of sterility were as follows: unilateral tubal closure 31.2 per cent, bilateral tubal closure 32.5 per cent, uterine hypoplasia 12.5 per cent and uterine malpositions and malformations 7.5 per cent. In 16.3 per cent of the cases no cause could be found.

Ten women (12.5 per cent) became pregnant within the first six months after the salpingography was done.

J. P. GREENHILL.

Palazzo, O. R.: A New Hysterographic Method, Arch. Clin. Obstet. y. ginec. 1: 460-466, 1942.

Palazzo recommends a new method for securing hysterograms. He uses a cannula at the end of which is a small balloon. After insertion into the uterus the balloon is distended with lipiodol so that after complete distention, the entire outline of the uterine cavity may be readily outlined on an x-ray picture. In this way no lipiodol escapes into the tubes or into the peritoneum. Furthermore, the author considers it beneficial that none of the lipiodol is wasted.

J. P. GREENHILL.

### Anatomy, Anomalies, etc.

Hirsch, Edwin F., and Martin, Mary E.: The Distribution of Nerves in the Adult Human Myometrium, Surg., Gynec. & Obst. 76: 697, 1943.

The distribution of nerves in the myometrium was studied in normal nulliparous human uteri by cutting serial sections and staining with selective stains. The nerves of the inner portion of the myometrium extend through the muscle and connect with the radial arteries. Large nerve trunks also enter the endometrium. These contain both myelinated and nonmyelinated fibers. Sensory and organs similar to pacinian corpuscles were found in the crevices of the muscle tissues, and more particularly in the adventitia of branches of the uterine artery.

L. M. HELLMAN.

Gray, Jessie: Successful Removal of a Sacral Parasitic Fetus, Canad. M. A. J. 47: 520, 1942.

A newborn infant with a sacrococcygeal teratoma is described. The incidence of this complication is estimated to be between one in 20,000 to 55,000 births. A prenatal x-ray was obtained because it was thought that two fetal heads were palpable.

CARL P. HUBER.

### Abortion

Dingle, Phillis: Two Cases of Renal Failure Following Abortion, J. of Obst. & Gynaec. Brit. Emp. 50: 246, 1943.

The author describes two cases of oliguria following abortion. One case had a severe pre-eclamptic toxemia, in whom the added trauma of induced delivery brought about shock and kidney dysfunction. The second case was that of a patient who fell, and probably had a traumatic accidental hemorrhage, which produced hematuria, shock and oliguria with azotemia. A recent survey of the literature lends weight to the fact that the etiology may be due to a damaged placenta.

WILLIAM BERMAN.

Paine, Alonzo K.: Progesterone in the Treatment of Threatened Abortion: A Review, Bull. New England M. Center 33: 39, 1943.

In a brief but timely article on the use of Progesterone in the treatment of threatened abortion, Dr. Paine calls attention to the extremely shaky evidence

upon which such therapy is based. The use of this substance for the prevention of threatened abortion presupposes that its action is to inhibit uterine contractions. While such may be the case for isolated muscle strips, it cannot be conclusively demonstrated by the uterine bag technique. The nullifying action of progesterone on pituitrin induced contractions, the author feels, is only of indirect value as far as the abortion problem is concerned. With experimental evidence, either negative or inconclusive, one is forced to examine the clinical evidence. At the onset there is some confusion as to the definition of threatened abortion, with a perfectly conceivable chance for error even if the most rigid criteria are adhered to. Dr. Paine calls attention to the fact that the literature on the subject is remarkable because of a total lack of reports of clinical failure when progesterone is used. The series of cases reported are usually small, and one is impressed by the fact that frequently symptoms are so mild that hospitalization of the patients was unnecessary. The difficulty is always the lack of adequate controls. The question, what would have happened with no therapy? Or with sedation alone? The conclusion of the author is that progesterone in the treatment of threatened abortion is, in the light of present knowledge, of little if any value.

L. M. HELLMAN.

Ludwig, F.: The Treatment of Imminent Abortion and Habitual Abortion With Corpus Luteum and Vitamin E, *Schweiz. med. Wchnschr.* 72: 1431-3, 1942.

The author reviewed the reports in the literature concerning the use of corpus luteum hormone and vitamin E in the treatment of imminent and habitual abortion. He found that the treatment of habitual abortion with corpus luteum yielded 89.4 per cent success, the treatment with vitamin E alone 79.7 per cent and the combined use of corpus luteum and vitamin E gave 91.3 per cent successful results. The articles failed to state how many of the cases might have ended successfully without the therapy.

The reports in the literature indicate that in the treatment of imminent abortion, corpus luteum yielded 61.7 per cent success, vitamin E 83.3 per cent, combined corpus luteum and vitamin E 76.9 per cent and treatment without corpus luteum or vitamin E gave 71.2 per cent success.

The author himself obtained only 58.3 per cent success in his own cases treated with corpus luteum and vitamin E. This is in contrast to the 76.9 per cent reported in the literature. The author emphasizes that to accomplish any results, large doses of progesterone must be given. In cases of threatened abortion large doses must be given within a short period of time, but in cases of habitual abortion, the doses are divided over a long period of time.

J. P. GREENHILL.

Brea, A. M.: Induced Abortion and Parturition by the Transparietal Uterine Route, *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 624, 1942.

The author discusses induction of abortion by the methods of Boero and Aburel and reports 14 cases. The method of Boero consists of transparietal puncture of the uterus, and that of Aburel of the injection of a saturated solution of sodium chloride. The Boero method usually does not produce immediate abortion and thus permits stabilizing the condition of the mother before subjection to obstetrical trauma. The method of Aburel is effective from the third month to the end of gestation.

Brea concludes from his own experience that these two types of induced abortion have special indications; that they are very efficient in some cases; that they should be used only by specialists, because of the dangers in the hands of un-



trained physicians; that in special situations disaster may follow, as with all other methods. That is, the ideal method of inducing abortion which does not have inherent dangers has not yet been found.

J. P. GREENHILL.

### Mammary Glands

Greene, E., and Caviedes, H.: Tuberculosis of the Breast and Its Coexistence With Cancer, *Rev. méd. de Chile* 71: 656, 1943.

The authors present two cases of mammary tuberculosis, in one of which adenocarcinoma was present. A 42-year-old multipara complained of pain of a month's duration in the upper internal quadrant of the right breast, where a small mass was felt. Sulfathiazole relieved the pain but had no effect on the mass. Physical findings otherwise were negative except for a few small axillary glands and retraction of the nipple. The preoperative diagnosis was fibro-adenoma with probable malignant degeneration. The pathologist reported tuberculous lesions with intense nonspecific inflammatory infiltration as well as hyperplastic epithelial lesions and foci of adenocarcinoma.

A 27-year-old woman noted a tumor the size of a nut in the areola, painless, retracting the nipple. A course of ultraviolet light was without effect. Ten months later, during an attack of the grippe the lesion became painful, red, lustrous and tense, accompanied by bilateral axillary adenitis which suppurated. The primary lesion was opened and drained with fistula formation. The breast was later removed and diagnosis of tuberculosis confirmed.

The literature on the subject is reviewed. Tuberculosis of the breast is rare and its coexistence with carcinoma extremely rare. Treatment of tuberculosis early is medical in the rare case in which it is diagnosed. Simple resection of the breast and axillary glands is advocated for advanced cases by the authors.

ROBERT J. WEISSMAN.

Müller, C.: Galactorrhea and Corpus Luteum, *Schweiz. med. Wchnschr.* 72: 1433-1434, 1942.

A case of galactorrhea is reported by the author in which all therapy failed. Laparotomy was finally resorted to and at operation, a persistent corpus luteum was found and removed. The flow of milk ceased. The menses which had ceased during the period of galactorrhea, started again. At the time of the report one year had elapsed since the operation. The patient's menses remained regular and the flow of milk remained in abeyance.

The author questions whether, in view of the fact that amenorrhea is nearly always associated with extrapuerperal lactation, a persistent corpus luteum does not play an important role. There are many cases of extrapuerperal galactorrhea where a pituitary or ovarian tumor is found. In such cases since medical therapy does not help, it is advisable to resort to a posterior colpotomy to search for a persistent corpus luteum.

J. P. GREENHILL.

Tolosa, Benedicto P. M.: Surgical Treatment of Puerperal Mastitis and Paramastitis, *Rev. de ginec. y obst.* 36: 157-173, 1942.

Benedicto P. M. Tolosa avoids the disadvantages of both small and large incisions by using the electric or Paquelin cautery. With the tip of the instrument heated to nearly white red, the site where the fluctuation is best perceived is punctured by a rapid stroke: several strokes may be needed to reach the abscess

when the wall of interposing tissues is thick. If the patient is not pusillanimous, anesthesia is not necessary because reapplication of the cautery does not cause great pain: the local nerve endings are destroyed at the first contact. An imperative precaution is not to leave the tip of the cautery in the tissues for any length of time: the spreading heat would destroy more tissue than necessary, and this would delay healing. The only aftertreatment needed is renewal of the dressing twice a day and gentle evacuating massage.

Thirty cases, mostly of parenchymatous mastitis, were treated in this manner: all started to heal in a few days and cicatrization was complete in two weeks. The esthetic result was excellent.

J. P. GREENHILL.

## Malignancies

Vespasiano Ramos, A.: Colpocytology As a Method of Diagnosing Cancer of the Uterus, *An. brasil. de ginec.* 15: 453-462, 1943.

The author gives a minute description of the normal cytology of the vagina and of the different types of cells identified by Papanicolaou and Traut as pathognomonic of cervical and body carcinoma. He emphasizes the simplicity of this procedure and its great convenience especially at the age when cancer is common. Lesions can be discovered at a time when the possibilities of therapeutic success are great.

J. P. GREENHILL.

Jones, Howard W., and Jones, Georgeanna E. Seegar: Panhysterectomy Versus Irradiation for Early Cancer of the Uterine Cervix, *J. A. M. A.* 122: 930, 1943.

The authors compare 704 patients treated at the Kelly Clinic with radium or x-rays or a combination of the two, with 36 cases treated by radical hysterectomy. The absolute cure rate for those operated upon was 41.6 per cent and that for the radiation cases was 57.5 per cent. These two groups are compared with reference to both clinical stage, and microscopic grading according to the method of Martzloff. Considering all stages of carcinoma, irradiation of the spinal cell cancers gives the poorest results. There is also reason to believe that adenocarcinoma of the cervix is the most favorable type for operation. In conclusion the authors state that "irradiation will prove more satisfactory for the entire squamous cell group, including the accidentally discovered and preinvasive lesions."

WILLIAM BERMAN.

Harvey, Roger A., and Ritchie, Robert N.: Carcinoma of the Cervix Complicated by Complete Procidentia, *Radiology* 41: 48, 1943.

The authors review the literature of the treatment of cancer of the cervix in procidentia and stress the value of radiation therapy in this condition especially where surgery is contraindicated. They review one of their own cases in an 81-year-old white female treated with radiation alone. It is felt that in tumors of this type, the use of small and controlled doses of roentgen rays will combat the infection, reduce the size of tumor, and thereby make it easier and more advantageous to use subsequent radium therapy. There seems to be some relief or cure of the procidentia by radiation therapy. In younger women and in any cases with evidence of extension of carcinoma, roentgen therapy to the exteriorized tumor should be followed by a full course of roentgen therapy to the pelvis and radium insertion for 5,000 to 6,000 milligram hours.

WILLIAM BERMAN.

Stromme, William B., and Traut, Herbert F.: Mesonephroma or Teratoid Adenocystoma of the Ovary, Surg., Gynec. & Obst. 76: 293-299, 1943.

Since the original report of Schiller in 1939, only 30 instances of mesonephroma of the ovary have been reported. To this the authors add ten cases in the present communication. The ages of the patients in the present report varied from 11 months to 68 years, however the majority were over 30 years of age. In eight cases the tumors were located in the left ovary. They varied from three to seventeen centimeters in the smallest diameter and on section presented multiple small cysts. The solid portions were pinkish-gray in color. The cysts yielded a shiny mucoid material.

The tumors were all slow in rate of growth and the usual complaints of the patients were related to a developing abdominal mass. Spread was by way of direct implantation of papillary structures, or by way of the lymphatics. The finding of abdominal fluid was rare; however, extensive bowel implantations were found. The more differentiated tumors were made up of closely packed structures resembling acini. The less differentiated they became the more the papillarity increased.

The authors were unable to demonstrate anything resembling a glomerulus and this fact has led them to disagree with Schiller in regard to the Wolffian duct origin of these tumors.

Six of the ten patients were dead within a year after operation. Neither surgery nor x-ray appeared to alter the course of the diseases.

F. M. HELLMAN.

### Cesarean Section

Sosa, Angel I., y Sanchez, and Nölting, David E.: Cesarean Section and Simultaneous Myomectomy, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 808-816, 1943.

The authors report 20 cases. In this group there were four deaths, one each from peritonitis, hemorrhage, collapse and shock and hemorrhage. When it is considered that cesarean section alone has a mortality rate between 1 and 2 per cent and postpuerperal myomectomy a rate between 2 and 4 per cent, it is immediately evident that the combination of these two procedures greatly increases the risks. Among the patients with pedunculated myomas, there were no deaths; but in those with intraligamentous growths, the mortality rate was 50 per cent.

From this experience and a review of the literature, the authors conclude that when a myoma is intramural or intraligamentous, and there is no ulceration or serious pressure on neighboring organs, cesarean section alone is the logical procedure. An exception to this can be made in the case of small or pedunculated myomas, where resection is simple, and in cases of generalized myomatosis, where hysterectomy is indicated. Although leaving the myoma increases the danger of necrosis or hemorrhage, this is compensated for by the immediate advantage of a more favorable postoperative course. Later another operation can be done to remove the tumor at a more favorable time for the patient.

The postoperative course of a woman subjected to cesarean operation is fraught with dangers due to the puerperal state, the effect of anesthesia, and of the operation itself because the uterine cavity is in communication with the abdominal cavity. These facts are substantiated by the morbidity and mortality statistics. If to these dangers are added those attendant on removal of myomas under conditions unfavorable for hemostasis and hence optimal for infection, it is easy to understand how the risks are multiplied.

J. P. GREENHILL.

## Gynecology

**Antunes, Altino, and Dutra, Licinio H.:** A Case of Brenner Tumor of the Ovary, *An brasil de ginec.* 7: 249-270, 1942.

According to the authors the tumor was of the solid type and was found in a Negress, aged 30, with polymenorrhagia and a firm swelling of the ovary. This is the third case of Brenner tumor to be reported from Brazil, and perhaps from South America. Based on reports in the literature, the authors discuss the incidence of Brenner tumor, the age incidence, pathology, histogenesis, classification and clinical characteristics. Their own case confirms the concept that Brenner tumors are fibroepithelial and benign, devoid of hormonal function and of any influence on ovulation. Examination of the portion of the ovary which adhered to the tumor disclosed the existence of ovarian follicles at various stages of evolution, including corpus-albicans, although no corpus luteum was found. The patient, who was still sexually active, gave a history of 4 induced abortions, which fact indicated that the presence of the tumor did not inhibit fertilization nor development of the ovum.

J. P. GREENHILL.

**Lordy, Carmo:** The Histogenesis of Walthard's Rests; Their Relation to Brenner Tumors of the Ovary, *An. brasil de ginec.* 7: 169-184, 1942.

In reviewing a case which the author reported 13 years previously under the title "Islands of interstitial cells within a fibroma of the ovary," he found that he was dealing with the solid type of Brenner tumor of the ovary. The structural peculiarities of the epithelial nests, particularly the presence of cylindrical mucous epithelium in their innermost part, around the central lacuna, were in complete agreement with Meyer's criteria of Brenner tumors. Based on a review of the embryologic development of the human ovary and on the histologic examination of the cortex of the ovary from a newborn puppy, the author has been able to prove the complete morphologic identity between the cells derived from the third proliferation of the covering epithelium of the ovary and the cells constituting Walthard's rests, the similarity of which to the epithelial nests of Brenner tumors is generally conceded today. He, therefore, concludes that, most likely, Brenner tumors were derived from epithelial rests originating during the third proliferation of the germinative epithelium, just as the masculinizing tumors of the ovary originate from cells of the first proliferation. The author was also able to confirm the presence of the median groove in the nuclei of the epithelium—described by Danforth as characteristic for Walthard's rests and Brenner tumors—in both his own case of Brenner tumor and in sections of the ovarian cortex of the newborn dog. He believes that these linear depressions and all their variants conform with the line of cleavage of the nucleus and correspond to the various stages of direct or amitotic division of the cell.

J. P. GREENHILL.

## Fibroids

**Coghlan, C. C.:** Conservative Treatment of Multiple Fibroid Tumours; Successful Pregnancy After Enucleation of 64 Fibroid Tumours of the Uterus, *M. J. Australia* 1: 346, 1942.

A cure is reported of a 24-year-old white unmarried female, upon whom myomectomy was performed. A total of 64 nodules, varying from  $2\frac{1}{4}$  inches to seedlings, were removed. Nearly 2 years later she was delivered of a living term-sized child by cesarean section. At the time of the second operation no mention was made of any recurrence of the myomas.

L. M. HELLMAN.

## Labor, Physiology, Management and Complications

Vautrin, Guillermo: Subcutaneous Symphysiotomy in an Incomplete and Complete Deflexion of the Head, *West. J. Surg.* 51: 389, 1943.

In this article there is revived the long debated value of subcutaneous symphysiotomy in obstetrics. The author reports 2 cases in which the operation was successfully performed under local anesthesia after very long labors. Failure to progress in these cases was due to incomplete deflexion of the fetal head. The technique of the operation is carefully described.

It is claimed that the anteroposterior diameter of the pelvis may be increased by 8 mm. The transverse diameter may be increased by 1 centimeter. One can expect spontaneous delivery in most cases following symphysiotomy and this occurred in the 2 cases reported. However, there is no contraindication to the use of forceps or pituitrin after the operation has been performed and the cervix is fully dilated. It is emphasized that immediate delivery after the operation is not necessary because the fetal heart often improves when the pressure has been relieved by symphysiotomy.

WILLIAM BICKERS.

McConnell, Graham, and Schaufler, Goodrich C.: Ergonovine by Vein During the Second Stage of Labor, *West. J. Surg.* 51: 403, 1943.

The use of ergonovine by vein during the second stage of labor is described. Various techniques in the management of the third stage, i.e., the use of posterior pituitary extract either before or after delivery of the placenta and the use of ergonovine following delivery of the placenta are compared with its routine use intravenously as the anterior shoulder engages under the symphysis. The chief objection raised against ergonovine, intravenously, as the anterior shoulder is being delivered is that incarceration of the placenta may ensue. The author emphasizes that this fear is rather exaggerated and that such anxiety should not precipitate hurried and unphysiologic methods of expression.

In the 142 cases studied, the average time between the intravenous injection of ergonovine and delivery of the placenta was 1 minute and 30 seconds. In the control group, using other techniques, the average time was 5 minutes and 40 seconds. Complications were few. Delayed post-partum hemorrhage occurred in 3 cases. One fatality occurred which could in no way be ascribed to the intravenous ergonovine. The administration of intravenous ergonovine is recommended in cesarean section.

WILLIAM BICKERS.

Browne, Francis J.: Reactions to Pressor Substances in Normal and Toxemic Women, *J. Obst. & Gynaec. Brit. Emp.* 50: 254, 1943.

The author studied normal women not pregnant (24 cases), normal pregnant women (20 cases), pregnancy with chronic hypertension (7 cases), and normal puerperal women (20 cases) with reference to the mean systolic rise in blood pressure after the injection of Tonephin (Bayer). The greatest increase occurred in the pre-eclamptic group (54 mm. Hg). It is felt that this may be due to a hypersensitivity characteristic of patients with chronic hypertension or of a woman who in later life will develop hypertension. A similar hypersensitivity is present in the patients with chronic hypertension especially where this hypertension existed before pregnancy. In pre-eclamptic toxemia, the reaction to the cold test was low, while in the hypertensives it was high. It was also noted that a high reaction was obtained in the puerperium of women who had had normal pregnancies. The cause of this increased sensitivity after delivery or its duration is not known.

WILLIAM BERMAN.

Torpin, Richard: Fibromyoma of the Cervix Uteri Obstructing Labor, West. J. Surg. 51: 196, 1943.

The author reports a case in which a 28-year-old white woman, para iii, gravida vi, was admitted to the hospital with the history of vaginal bleeding. On examination the uterus was found to be rigid and the diagnosis of premature separation of the placenta was made. Attempt to rupture the membranes failed because of an obstructing fibroid in the cervix, measuring 10 by 11 cm. A total hysterectomy was done using the method of primary ligation of the ovarian and uterine arteries. Pathological examination revealed a tumor arising from the cervix posteriorly, displacing the fetal head forward over the symphysis. A dissecting hematoma was found between the placenta and uterine wall. A classification for cervical fibromyoma is suggested.

WILLIAM BICKERS.

# Society Transactions

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## THE OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF OCTOBER 7, 1943*

Case Reports: Repeated Hydatidiform Mole Followed by Chorionepithelioma. Eleanor H. Balph, M.D.

Eclampsia, Cerebral Abscess and Hemorrhage. S. Leon Israel, M.D., and Bernard J. Alpers, M.D. (by invitation). (For original article, see page 551.)

The following papers were presented:

Carcinoma of the Cervix, End Results. Charles A. Behney, M.D., and John Y. Howson, M.D. (For original paper, see page 506.)

Biologic Characteristics of the Normal Vagina. A. E. Rakoff, M.D., Louis G. Feo, M.D., and Leopold Goldstein, M.D. (For original paper, see page 467.)

*MEETING OF NOVEMBER 4, 1943*

Paper: Gynecological Endocrinopathies of Early Life. Emil Novak, M.D. (by invitation).

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## THE CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF NOVEMBER 19, 1943*

The following paper was presented:

The Effect of the Interval Between Births on Maternal and Fetal Outlook.

Nicholson J. Eastman, M.D. (by invitation). (For original article, see page 445.)

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## THE PITTSBURGH OBSTETRICAL & GYNECOLOGICAL SOCIETY

Regular meeting held Monday, October 11, 1943.

The Voorhees Bag in Modern Obstetrics. H. A. Power, M.D., and H. Erving, M.D. (by invitation). (For original article, see page 527.)

## Items

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### The Passano Foundation, Incorporated

The objects of the Foundation as set forth in its charter are: "For scientific and educational purposes, particularly to provide for scientific research and to publish the results of scientific research and to make awards for meritorious achievements in scientific research."

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School is a director of the Foundation, also Dr. George Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington. Mr. Robert S. Gill, President of The Williams & Wilkins Company, has been elected President of the Foundation and Mr. George Hart Rowe, of The Williams & Wilkins Company is a director. Headquarters are at Mt. Royal and Guilford Avenues, Baltimore (2), Md.

Mr. E. B. Passano, for whom the Foundation is named, is Chairman of the Board of The Williams & Wilkins Company.

By the terms of the charter of the Foundation, the Board of Directors may inaugurate the establishment of an annual award not to exceed \$5,000 for the outstanding contribution to the advancement of medical science made within the year by an American citizen.

A number of other projects are under consideration. One is the advancement of postgraduate instruction among physicians in sections of the country not accessible to medical centers in the larger cities.

As indicated, the declared purpose of the Foundation is broad and consideration will be given to any activity within its limits.

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### Color Films

The motion picture in color, "Continuous Caudal Analgesia in Obstetrics," which was made available by Eli Lilly and Company, Indianapolis, for showing before medical societies and hospital staffs, has been in continuous demand since release several months ago. It was made at the U. S. Marine Hospital, Staten Island, by authorization of the Surgeon General, U. S. Public Health Service, and the demonstrations were carried out by Drs. Hingson and Edwards, originators of the technique.

The three films that were made at the Nutrition Clinic of the University of Cincinnati in the Hillman Hospital, Birmingham, Alabama, under the joint auspices of the Department of Internal Medicine at the University of Cincinnati and the University Hospitals of Cleveland have likewise been in constant circulation. One of these deals with thiamin chloride deficiency, the second with nicotinic acid deficiency, and the third with ariboflavinosis.

None of the films contain advertising. They are available to physicians for showing before medical societies and hospital staffs.

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### American Board of Obstetrics and Gynecology, Inc.

#### Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Wednesday, June 7, through Tuesday, June 13, 1944. The Hotel William Penn in Pittsburgh



will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 15, 1944.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1945 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

PAUL TITUS, M.D.

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## Necrology

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HERMAN EMIL HAYD, M.D., F.A.C.S., M.R.C.S. (England), a member of the Advisory Editorial Board of the JOURNAL in its earlier years, Consulting Surgeon to the Memorial and Deaconess Hospitals of Buffalo, President of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons in 1911, died in Buffalo, where he had practiced his specialty and had been a resident for many years, February 18, 1944, at the age of 85.

# ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 842 Park Ave., New York, N. Y. Annual meeting Hershey, Pa., June 19-21, 1944.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting not announced.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting Chicago, June 12-16, 1944.
- New York Obstetrical Society.** (1863) *President*, W. T. Kennedy. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Catharine Macfarlane. *Secretary*, J. B. Montgomery, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, George H. Gardner. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, James P. McMannus. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, David B. Ludwig. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

- New England Obstetrical and Gynecological Society.** (1929) *President*, Frank A. Pemberton. *Secretary*, Fred. J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, J. Keith Cromer, 1835 Eye St., N.W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napolcon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, R. Glenn Craig. *Secretary*, D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Norman F. Miller. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Gerhard Ahnquist, 1336 Madison Street, Seattle. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Meehler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, Geo. D. Huff. *Secretary*, Frank Russell, 233 A St., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, John D. Graham, Devil's Lake. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

# American Journal of Obstetrics and Gynecology

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## Original Communications

### SOME OBSERVATIONS ON THE HORMONAL CONTENT OF OVARIAN CYSTS ASSOCIATED WITH PREGNANCY\*

RUTH M. WATTS, PH.D., AND FRED L. ADAIR, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)*

THIS report is a part of a general study<sup>1, 2</sup> of the relationship of hormones to ovarian tumors and is an attempt to correlate the occurrence of hormones in the cyst fluid with the histology of the tumor. A previous report<sup>2</sup> was concerned with the occurrence of estrogen in the cyst fluids of benign and malignant ovarian tumors from nonpregnant patients. Because of certain hormonal implications the cysts associated with pregnancy were omitted from that study and are the subject of this report.

There are few references in the literature to the occurrence of hormones in ovarian cysts associated with pregnancy. (Table I.) The presence of estrogen was reported by Allen, Pratt, Newell and Bland<sup>3</sup> Philipp<sup>4</sup> and Geller<sup>5</sup> but it was not found by Moulouguet<sup>6</sup> and Lepper, Pratt, Pratt and Vaux.<sup>7</sup> Gonadotropin was found by Zondek,<sup>8</sup> Philipp,<sup>4</sup> Geller<sup>5</sup> and Lepper et al.<sup>7</sup> In corpus luteum cysts associated with hydatidiform mole and chorionepithelioma, Siegmund,<sup>9-11</sup> von Probstner<sup>12</sup> and Zondek<sup>13</sup> found both estrogen and gonadotropin; Ruzieska,<sup>14</sup> McLaughlin<sup>15</sup> and de Alvarez<sup>16</sup> reported the presence of gonadotropin and Allen<sup>17</sup> the presence of estrogen. The hormonal content of human corpora lutea of pregnancy has been investigated by Allen, Pratt and Doisy,<sup>18</sup> Gillman and Smyth<sup>19, 20</sup> and Gluckman.<sup>21</sup>

\*This work has been supported by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. HORMONAL CONTENT OF CYST FLUIDS

INVESTIGATOR	TYPE OF CYST	PERIOD OF PREGNANCY	AMOUNT OF FLUID IN CYST (c.c.)	GONADOTROPIN	ESTROGEN
OVARIAN CYSTS ASSOCIATED WITH PREGNANCY					
Moulounguet (1928)	Corpus luteum	Post partum	0.5		Negative in rats
Allen, Pratt, Newell and Bland (1930)	Corpus luteum	2 to 3 mo.	17.5		
Zondek (1931)	Pseudomucinous	8 wk.	500	1 M.U. per c.c.	0.5 c.c. positive in rats
		6 wk.	65	80 M.U. Prolan A; 130 M.U. Prolan B	
Philipp (1934)	Pseudomucinous	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Serous	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Corpus luteum	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
	Corpus luteum	2 to 4 mo.		2.6 c.c. positive in mice	3 c.c. positive in mice
Geller (1934)	Serous	4 mo.	17 L	Positive in mice	Positive in mice
Lepper, Pratt, Pratt, and Vaux (1938)	Pseudomucinous	23 wk.		48 c.c. positive in rabbit	8 to 12 c.c. neg. in rats
	Lutein	12 wk.		48 c.c. positive in rabbit	8 to 12 c.c. neg. in rats
	Germinal	18 wk.		20 c.c. sl. positive Prolan A and neg. Prolan B in rabbit	8 to 12 c.c. neg. in rats
OVARIAN CYSTS ASSOCIATED WITH HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA					
Siegmund (1931)	Corpus luteum			500,000 M.U. per L	10,000 M.U. per L
Siegmund (1932)	Corpus luteum			1.2 to 2.4 c.c.; strongly positive Prolan A; weakly positive Prolan B	>10,000 M.U. per L
Siegmund (1934)	Corpus luteum			>200,000 M.U. per L	>2,000 M.U. per L
	Corpus luteum			1,000 M.U. per L	>2,000 M.U. per L
	Corpus luteum			<20,000 M.U. per L	
	Corpus luteum			Positive	Small amount
von Probstner (1935)	Corpus luteum (bilateral)			Prolan B strongly positive	
Ruzicka (1935)	Corpus luteum			5,000 M.U. per L	26 c.c. positive in rats
Allen (1940)	Corpus luteum (bilateral)			Large amount	
McLaughlin (1941)	Corpus luteum (bilateral)			Strongly positive	
de Alvarez (1942)	Corpus luteum			5,500 M.U. Prolan A; 550 M.U. Prolan B per L	2,000 M.U. per L
Zondek (1942)	Corpus luteum		260 (total)		
			30		
PAROVARIAN CYSTS ASSOCIATED WITH PREGNANCY					
Zondek (1931)	Parovarian	8 wk.	145	Negative	
Kittner (1933)	Parovarian	8 wk.	140	1.2 to 2.4 c.c. positive in mice	
Philipp (1934)	Parovarian	2 to 4 mo.		2.6 c.c. Prolan positive in mice	3 c.c. positive in mice
Pardini (1941)	Parovarian		550	6 c.c. negative in rabbit	
	Parovarian		8	6 c.c. negative in rabbit	
	Parovarian		2500	6 c.c. negative in rabbit	
	Parovarian		30	6 c.c. negative in rabbit	

Philipp<sup>4</sup> reported the presence of both estrogen and gonadotropin in the fluid of a parovarian cyst associated with pregnancy; gonadotropin was found by Kittner<sup>22</sup> but not by Zondek<sup>8</sup> and Pardini.<sup>23</sup>

We have investigated the estrogen content of the cyst fluids from 30 ovarian cysts, 3 parovarian cysts and 2 other genital cysts associated with pregnancy. The gonadotropin content was studied in a few of these. Gonadotropin was generally present but estrogen was not always found. This may be due to a failure of the hormone to be stored in the cyst fluid or to the fact that the tumors were usually removed early in pregnancy when the estrogen level is comparatively low.

### Methods

The ovarian tumors were received directly from the operating room and described. The fluid was aspirated from each cyst cavity and a specimen of tissue removed from the wall of each cavity for histologic examination. In multilocular tumors the different locules are designated by letters; e.g., cyst No. 277 had 3 cyst cavities, namely, A, B and C. Because of the small amounts of material available for study strictly quantitative assay of the hormonal content could not be made; therefore, the values are expressed in rat units based on the smallest amount of material which gave a positive response or the largest amount tested which gave a negative response.

*Estrogen.*—When fluids were tested without extraction the fluid was injected subcutaneously into ovariectomized adult albino rats, in three doses during an eight-hour period, and the vaginal smears read at 48 and 56 hours. When it was possible or desirable to test large amounts of fluid, extracts were made according to a method<sup>2</sup> previously described and involving alcohol precipitation, evaporation in vacuo, acidification and extraction with ether. Extracts were made up in olive oil and administered subcutaneously in one dose. Fluids were not tested at higher levels than 200 c.e. per dose. Wherever possible, at least three extracts were made.

*Gonadotropin.*—Fluids were tested for gonadotropin in 21-day-old male or female rats. The fluid was injected subcutaneously twice daily for three days, the animals were sacrificed at 96 hours, and either the weight response of the seminal vesicle or the blood point response in the ovary was used as the criterion of a positive response.

*Histology.*—The tissues were fixed in formalin and stained with hematoxylin and eosin.

### Clinical Material

In the present study there are 30 cases of ovarian cysts associated with pregnancy; in 23 cases (76.7 per cent) the cysts were removed during pregnancy and in seven cases, during the post-partum period. The 16 cases mentioned briefly in our first report are included in this series. In a previous paper<sup>2</sup> we reported hormonal studies of the cyst

fluids of 189 cases of benign ovarian cysts not associated with pregnancy. For purposes of comparison a group of these patients has been used as a control group in this report. This group consists of 114 patients with single type ovarian tumors (only one type of cyst present) and excludes patients with multiple type tumors (more than one type of cyst present), bilateral tumors and those which are the second occurrence of an ovarian tumor in the same patient.

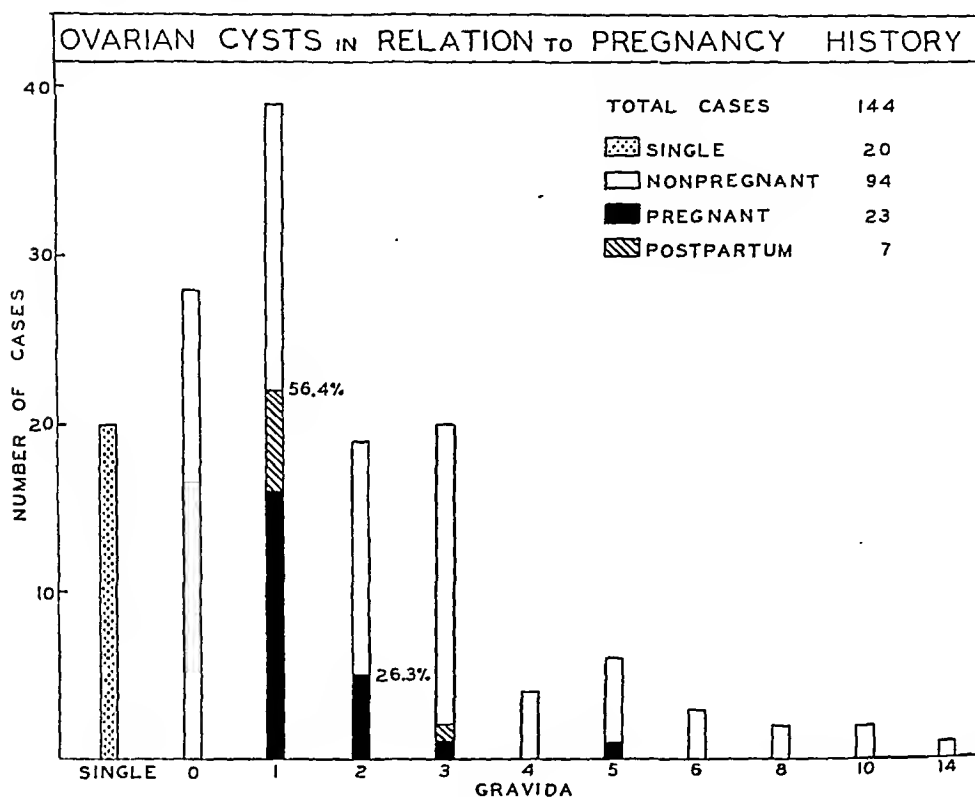


Fig. 1.

### Classification of Ovarian Cysts

All of the ovarian cysts were benign. They were classified as follicle and corpus luteum cysts (pseudoneoplasms), simple serous, papillary serous, pseudomucinous and dermoid cysts.

### Pregnancy History

In the total group of 144 ovarian cysts upon which hormonal studies have been made, 114 were in nonpregnant patients (previously reported<sup>2</sup>) and 30 were associated with pregnancy. In the entire group, 33.3 per cent (48 cases) were found among single women (20 cases) and married women (28 cases) with no history of pregnancy; 66.7 per cent (96 cases) were among patients with a history of 1 or more pregnancies. About one-fifth of the cases (30 cases) was associated with a pregnancy; in 23 cases (16 per cent) the cysts were removed during pregnancy and in seven cases (4.9 per cent) in the post-partum period. In

the group of 96 cases with histories of one or more pregnancies, 39 patients (40.6 per cent of the group or 27.1 per cent of the entire series) gave a history of one pregnancy; the cysts were associated with the pregnancy in 56.4 per cent of the cases (22 cases) and there was no relation to a pregnancy in 43.6 per cent (17 cases). Of the 22 cysts associated with the first pregnancy, 16 were removed during pregnancy and six in the post-partum period; 73.3 per cent of the cysts (22 of 30) associated with pregnancy were in primiparous patients. Of the entire series, 13.2 per cent (19 cases) gave histories of two pregnancies; in 26.3 per cent of these (5 cases) the cysts were removed during pregnancy, and 73.7 per cent (14 cysts) were not associated with the pregnancy. In two cases cysts were associated with the third pregnancy and in one with the fifth pregnancy. (Fig. 1.)

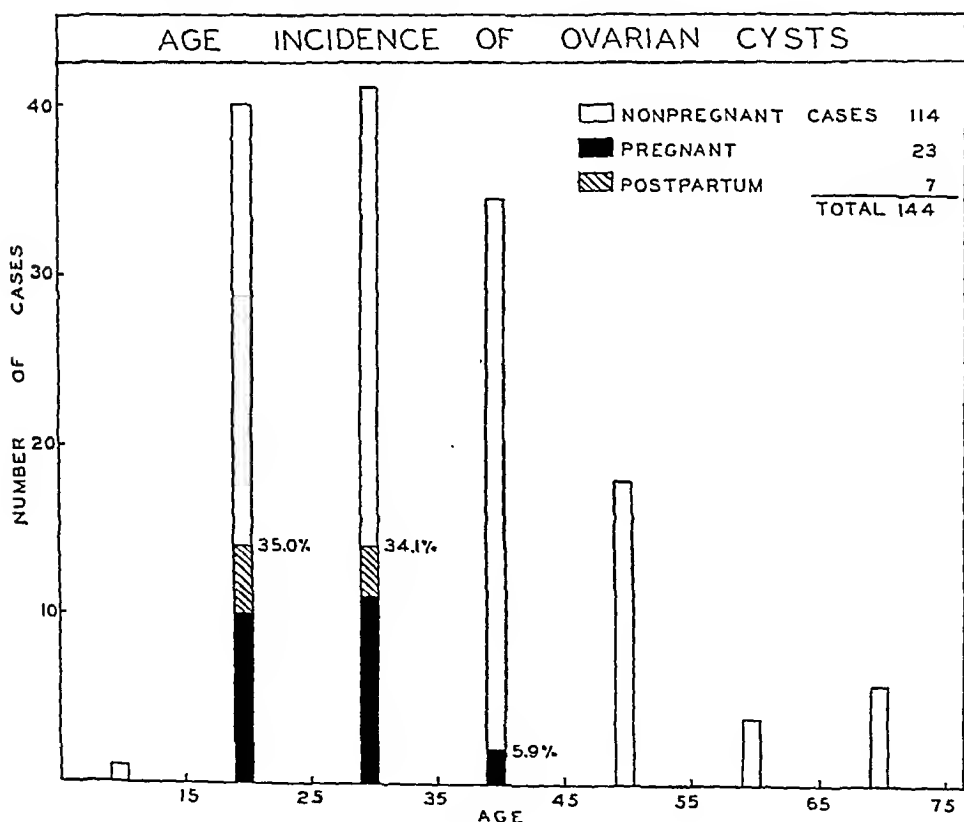


Fig. 2.

### Age Incidence

In the same group of 144 cases of ovarian cysts, 114 cases were among nonpregnant patients and 30 cases were associated with pregnancy. The ages at which these cysts occurred are shown by decades 15 to 24, 25 to 34, etc., in Fig. 2. In this series 79.9 per cent (115 cases) occurred in the three decades, 15 to 44 years, and the distribution was approximately the same in each of these decades, 27.8 per cent, 28.5 per cent and 23.6 per cent, respectively. The two decades, 15 to 24 and 25 to 34



years, include 56.3 per cent (81 cases) of all the cases and 93.3 per cent (28 cases) of the cysts associated with pregnancy. There were 14 cases associated with pregnancy in each of these decades or 35.0 per cent and 34.1 per cent, respectively, of the cysts occurring in those decades.

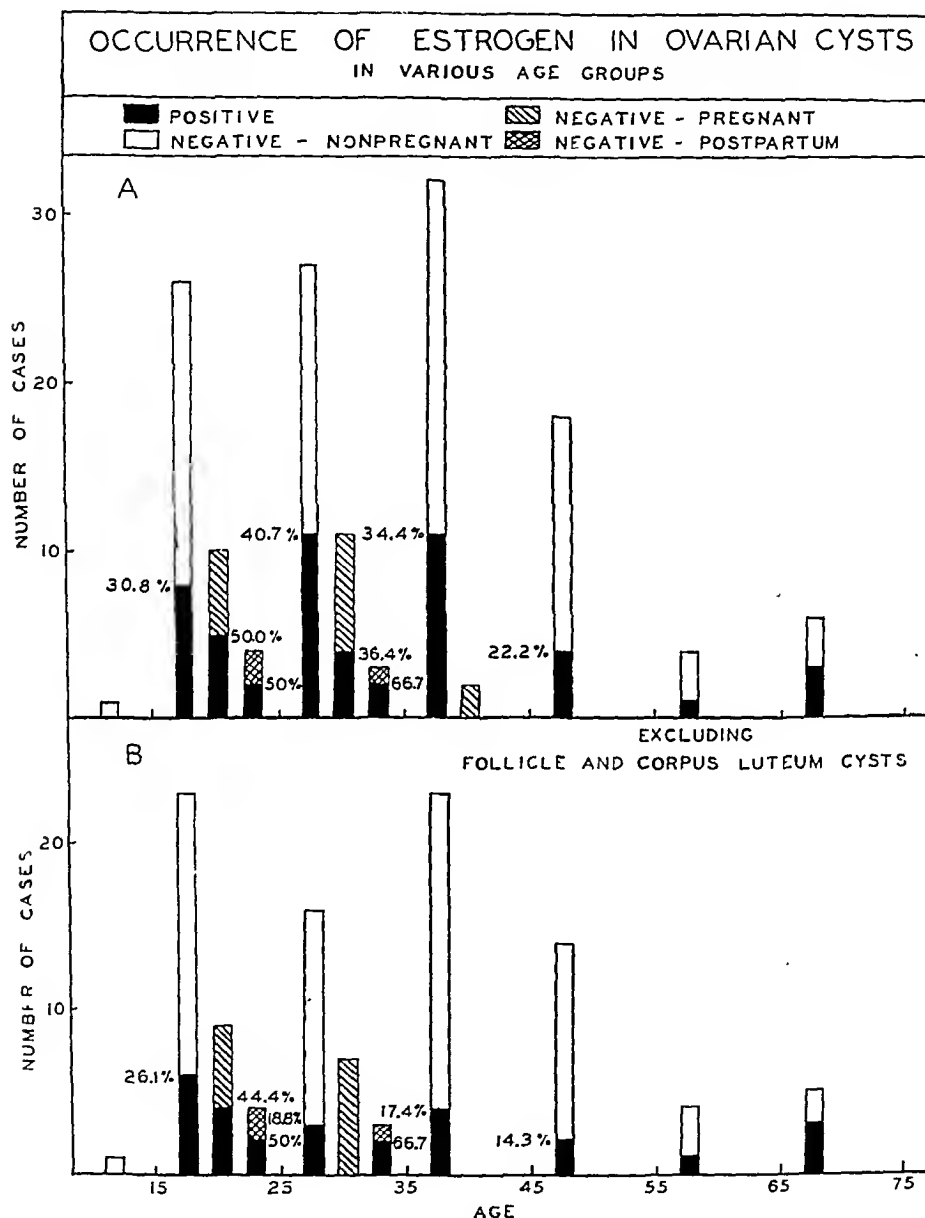


Fig. 3.

### Occurrence of Estrogen in Ovarian Cysts in Various Age Groups

Occurrence of estrogen in ovarian cysts in various age groups is shown in Fig. 3A. In the decade 15 to 24 years, 30.8 per cent (8 of 26 cysts) in the nonpregnant patients, 50 per cent (5 of 10 cysts) in the pregnant patients and 50 per cent (2 of 4 cysts) removed from patients in the post-partum period contained estrogen. In the following decade, 25

to 34 years, 40.7 per cent (11 of 27 cysts) from nonpregnant patients, 36.4 per cent (4 of 11 cysts) from pregnant patients and two of three cysts removed post partum showed estrogen.

Since follicle and corpus luteum cysts are expected to contain estrogen, cysts of these types were excluded from the data appearing in Fig. 3B. There were no follicle cysts in the pregnancy group. These data include 86 cases from the series of nonpregnant patients and 23 cases in which the cysts were associated with pregnancy. In the decade, 15 to 24 years, 26.1 per cent (6 of 23) of the cysts in nonpregnant patients, 44.4 per cent (4 of 9) of the cysts removed during pregnancy,

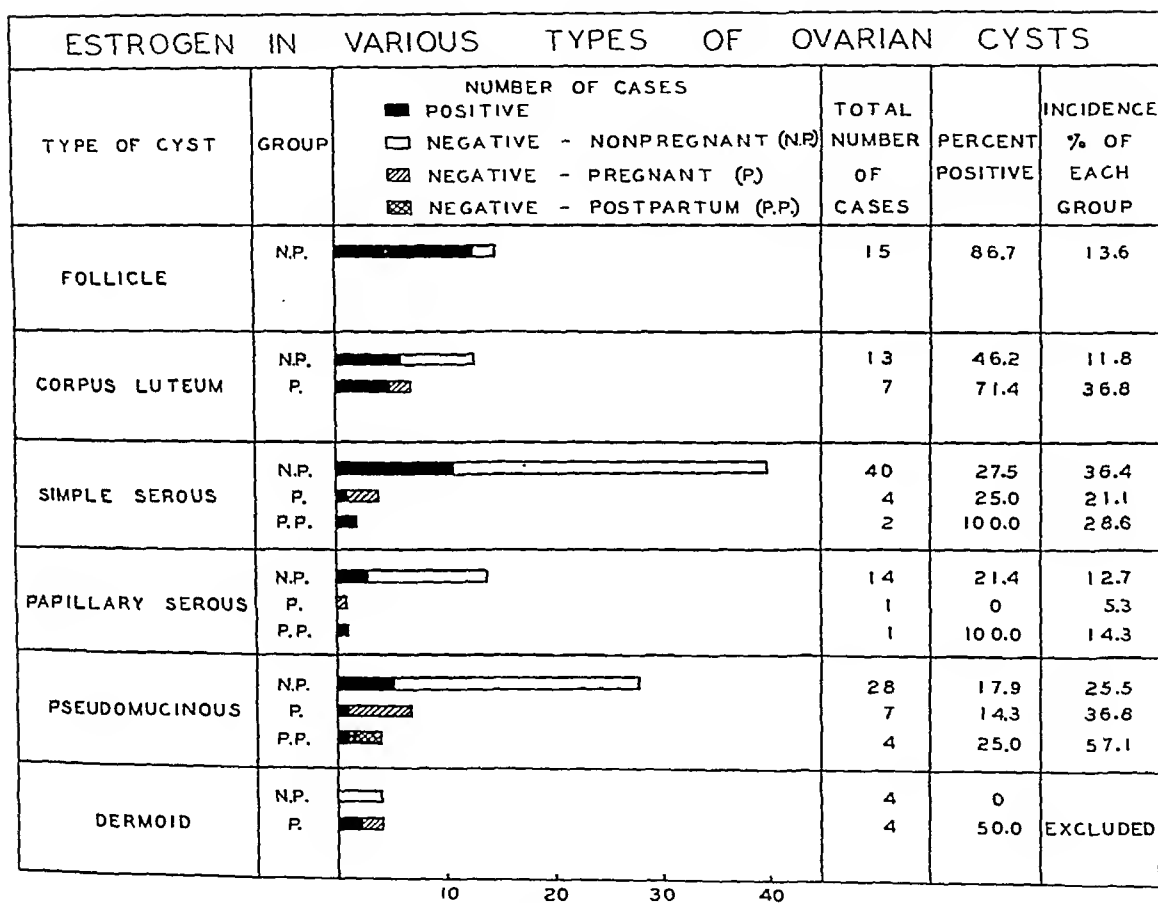


Fig. 4.

and 50 per cent (2 of 4) removed post partum contain estrogen. In the decade, 25 to 34 years, 18.8 per cent (3 of 16) of the cysts in nonpregnant patients, none in pregnant patients and 66.7 per cent (2 of 3) of the cysts removed post partum contained estrogen.

#### Incidence of Various Types of Cysts

The incidence of the various types of ovarian cysts is shown in Fig. 4. Because of the nature of dermoid cysts and the type of cyst contents not all dermoids were tested for hormone. Consequently, they are excluded in determining the incidence of the series. In the group of 110

cysts removed from nonpregnant patients the incidence was: follicle, 15 (13.6 per cent); corpus luteum, 13 (11.8 per cent); simple serous, 40 (36.4 per cent); papillary serous, 14 (12.7 per cent); pseudomucinous, 28 (25.5 per cent). In the group (19) removed during pregnancy the incidence was: follicle, none; corpus luteum, 7 (36.8 per cent); simple serous 4 (21.1 per cent) papillary serous 1 (5.3 per cent); pseudomucinous 7 (36.8 per cent). In the group of 7 cysts removed in the post-partum period the incidence was: follicles, none; corpus luteum, none; simple serous, 2 (28.6 per cent); papillary serous, 1 (14.3 per cent); pseudomucinous, 4 (57.1 per cent). Considering the entire group of 26 cysts (excluding dermoids) associated with pregnancy, the incidence of corpus luteum cysts (26.9 per cent) and of pseudomucinous cysts (42.3 per cent) seems higher than in the nonpregnant group and that of simple serous (23.1 per cent) and of papillary serous (7.7 per cent) seems somewhat lower. However, the series is too small to draw definite conclusions.

### Occurrence of Estrogen in Ovarian Cyst Fluids

For the various types of cyst fluids in the group of 114 single type cysts, previously reported,<sup>2</sup> the percentages of the cysts which contained estrogen were as follows: follicle, 86.7 per cent (13 of 15 cysts); corpus luteum, 46.2 per cent (6 of 13 cysts); simple serous, 27.5 per cent (11 of 40 cysts); papillary serous, 21.4 per cent (3 of 14 cysts); pseudomucinous, 17.9 per cent (5 of 28 cysts). In the group of 23 cysts removed during pregnancy the percentages of the various types which contained estrogen were: no follicle cysts; corpus luteum, 71.4 per cent (5 of 7 cysts); simple serous 25 per cent (1 of 4 cysts); papillary serous (one negative); pseudomucinous, 14.3 per cent (1 of 7 cysts); dermoid, 50 per cent (2 of 4 cysts). In the group of 7 cysts removed post partum there were no follicle or corpus luteum cysts; 2 simple serous cysts, one papillary serous cyst and one of four pseudomucinous cysts contained estrogen. In the entire group of cysts associated with pregnancy, the percentage of cysts containing estrogen was 43.3 per cent in contrast to 33.3 per cent of positive cysts in the nonpregnant patients. (Fig. 4.)

When the cysts commonly containing estrogen, namely, follicle and corpus luteum cysts, are excluded, 34.8 per cent of the cysts associated with pregnancy and 22.1 per cent of the cysts not associated with pregnancy contain estrogen. Estrogen was found in 25 per cent of the cysts (4 of the 16 cysts) removed during pregnancy and 57.1 per cent (4 of 7 cysts) removed post partum.

In general, the amount of estrogen found is about that reported previously.<sup>2</sup> In the corpus luteum cysts removed during pregnancy the amount of estrogen found ranged from 0.07 to 2.5 R.U. per e.e. and in cysts from nonpregnant patients previously reported ranged from 0.12 to 2 R.U. per e.e. This is probably less than the amount found by

Allen, et al.<sup>18</sup> in the fluids of corpora lutea of nonpregnant patients or human corpora lutea of pregnancy. One simple serous cyst contained 0.33 R.U. per c.c.; in one pseudomucinous cyst, No. 210, one fluid showed 0.005 R.U. per c.c. and one, 0.01 R.U. per c.c., and two others showed less than 0.03 and 0.05 R.U. per c.c., respectively. Fluids from two dermoids were negative; from another the fluid showed 0.005 R.U. per c.c.; the two fluids from another dermoid cyst, No. 226, showed 0.02 R.U. per c.c. in one fluid and less than 0.06 R.U. per c.c. in the other.

The failure to find estrogen in all cysts during pregnancy may be due to the small amount of fluid available for testing or to the fact that many cysts were removed early in pregnancy when the estrogen level is comparatively low. Although more cysts from post-partum patients contain estrogen they do not contain unusual amounts of this hormone, and the tumor probably does not act as a hormonal depot. (Table II.)

### Occurrence of Gonadotropin in Ovarian Cyst Fluids

Not all cyst fluids were tested for gonadotropin. Fluid from two pseudomucinous cysts, No. 28 and No. 64, each showed 0.25 R.U. per c.c., and the fluid of another pseudomucinous cyst, 210A, showed 0.67 R.U. per c.c. The tumors were removed during the twelfth, seventeenth, and twenty-eighth week of pregnancy, respectively. One simple serous cyst, No. 3, removed one week post partum, contained fluid showing 0.25 R.U. per c.c. Considering the amount of gonadotropin circulating in the body during pregnancy, it is not surprising to find it in the cyst fluid. However, the concentration is considerably lower than is found in blood serum in pregnancy. Thirteen cyst fluids from ovarian tumors occurring in nonpregnant patients were tested for gonadotropin but amounts varying from 1 to 18 c.c. were negative.

### Miscellaneous

Fluid was removed from the corpus luteum in two cases (No. 44 and No. 115) in which pregnancy was interrupted because of cardiac disease. These were not included in the general series because no tissue was obtained for histologic control. One fluid contained less than 1.11 R.U. per c.c. of estrogen and the other 0.33 R.U. per c.c.

A case with a placental polyp was studied. Because of a suspicion of malignancy, hysterectomy and bilateral oophorectomy were performed. Both ovaries contained cystic follicles; the right ovary, No. 135, contained 5 c.c. and the left, No. 136, 5.4 c.c. (composite specimen). Fluid from the right ovary contained 5 R.U. per c.c. of estrogen and less than 0.83 R.U. per c.c. of gonadotropin; the left ovary showed less than 1.67 R.U. per c.c. of estrogen and 5 R.U. per c.c. of gonadotropin. There was little epithelial lining on the wall of the follicles in the left ovary, showing no estrogen. The endometrium showed actively growing chorionic tissue.

TABLE II. HORMONAL CONTENT OF CYSTS ASSOCIATED WITH PREGNANCY

TYPE OF CYST	CYST NO.	AMOUNT OF CYST FLUID		ESTROGEN C.C. FLUID +	R.U. PER C.C.	GONADO-TROPIN		R.U. PER C.C.	CLINICAL OBSERVATIONS				REMARKS
		C.C.	FLUID			C.C.	FLUID		AGE	GRAV. PREG.	WK.	DELIVERY	
OVARIAN CYSTS REMOVED DURING PREGNANCY													
Corpus luteum (7)	23	96.5		3		0.33			33	1	7	Ectopic	Laparotomy
	65	20.5		0.4		2.50			25	2	3	Ectopic	Laparotomy
	114	60			50	<0.02			39	1	36	Ces. sect.	Twisted pedicle, necrotic, gangrenous
	122	1.5			1	<1.00			35	2	11	Natural	Diabetes
	223	92		15		0.07			30	1	16	Natural	Pre-eclampsia
	277 A	189.5		3		0.33			23	1	10	Forceps	Progestin for 2 weeks, postoperative
	B	51		5		0.20							
	C	2.4			1.5	<0.67							
	280	35		3		0.33			33	5	10	Ab. 5 mo.	Progestin for 2 days, postoperative
Simple serous (4)	120	135			45	<0.02			28	1	18	40	Natural
	212	174		3		0.33			23	1	8		
	265	310			200	<0.005			29	1	13	40	Forceps
	287 A	180			115	<0.009			26	1	15	39	Forceps
	B	34			26	<0.04							
Papillary serous (1)	228	31			10	<0.10			29	1	22	38	Natural
Pseudomucinous (7)	28	600			100	<0.01		4	28	1	12	40	Natural
	64	380			100	<0.01		4	25	1	17	39	Natural
	148	160			145	<0.007			19	1	17	40	Natural
	167	400			200	<0.005			23	3	20	40	Natural
	210 A	>6135		200		0.005		1.5	23	1	28	40	Natural
	B	25			20	<0.05							
	C	38			32	<0.03							
	D	97		80		0.01							
	283 A	4025			200	<0.005			23	1	13	40	Forceps
	B	34			30	<0.03							
	C	17			15	<0.07							
	294 A	81			67.5	<0.02			33	2	39	39	Ces. sect.
	B	35			31.3	<0.03							

Dermoid (+)	34	2150	112	<0.009	22	1	10	Missed ab.
	95	428	200	0.005	21	1	11	Forceps
	169	594	200	<0.005	30	2	11	Natural
	226 A B	6780 38	50 17	0.02 <0.06	21	2	17	Natural
OVARIAN CYSTS REMOVED POST PARTUM								
Simple serous (2)	3	3050	4	0.25	26	1	1 PP	Forceps
	250	4026	25	0.04	23	3	2½ PP	Natural
Papillary serous (1)	211	1065	125	0.008	24	1	9 PP	Natural
Pseudomucinous (+)	38	3810	150	<0.007	28	1	5 PP	Induced
	73	416	150	<0.007	23	1	8 PP	Natural
	144	850	200	<0.005	21	1	13 PP	Delivered elsewhere
	291	2280	200	0.005	28	1	5 PP	Twisted; tumor for 8 years
MISCELLANEOUS								
Corpus luteum	44	2.2	0.9	<1.11	42	3	9	Cardiac; laparotomy
	115	18	3	0.33	27	1	13	Cardiac; laparotomy
	135	5	0.2	5	32	3	4	Missed ab.
	136	5.4	0.6	<1.67	5			Placental polyp; bilateral cysts
NONOVARIAN CYSTS REMOVED DURING PREGNANCY								
Parovarian	17	56	15	0.06	30	1	39	Twisted pedicle
Parovarian	102	178	25	<0.04	32	5	4° PP	Ruptured uterus
Parovarian	255	48	32	<0.03	28	3	10	Meningo-encephalitis 2 years before
Gartner's duct	P2	13.5	13	<0.08	22	2	30	Natural
Cystic fibroid	P9	51	15	0.06	41	1	39	Porro C.S.

Of the seven corpus luteum cysts two were associated with ectopic pregnancies, one patient aborted, one was delivered by cesarean section, one by forceps and two delivered naturally. In 16 patients with other types of cysts removed during pregnancy, there was one case of missed abortion, four cases of delivery by forceps, one case with cesarean section, nine cases with natural delivery and one case was not followed.

### Nonovarian Cysts

Fluids from three parovarian cysts associated with pregnancy were tested for estrogen; one cyst, No. 17, contained 0.06 R.U. per c.e. and two others, No. 102 and No. 255, contained less than 0.04 and 0.03 R.U. per c.e., respectively. Parovarian cyst No. 17 contained less than 0.13 R.U. per c.e. of gonadotropin. Fluid from a cyst of Gartner's duct contained less than 0.08 R.U. per c.e. of estrogen. Fluid from a cystic fibroid contained 0.06 R.U. per c.e. of estrogen and 10 R.U. per c.e. of gonadotropin. Twenty-six of the 27 fluids of nonovarian cysts previously reported<sup>2</sup> were negative and fluid from one parovarian was positive for estrogen.

### Comments\*

Considering the part the ovary plays in the endocrine system, it is of interest to consider what role hormones might play in the etiology and development of ovarian tumors. In this study we have attempted to correlate the histology of the tumor, especially of the lining of the cyst cavity, with the hormonal findings of the cyst fluid. Considering the multiplicity of the component parts of the ovary, both endocrine and otherwise, and the intricate mechanisms involved in the rapid and successive changes which take place, it is not surprising that the ovary gives rise to a variety of pathologic developments and to neoplasms. It is of interest to consider what might happen should any one of these mechanisms fail or the hormonal state be altered by pregnancy.

In view of the striking effects on the ovary of gonadotropin from various sources, it might be possible to infer excessive hormonal stimulation as a possible contributing factor, at least, in certain types of pathologic conditions in the ovary. Such effects have been produced in both experimental animals and in human beings.<sup>24-29</sup> Furthermore, this view might be supported by the high incidence of lutein cysts associated with hydatidiform mole and chorionepithelioma.<sup>30-32</sup> In these conditions the high level of gonadotropin is believed to be responsible for the luteinization of the ovary and regression<sup>32</sup> has been observed following the removal of the mole. Since gonadotropin may be present in early pregnancy<sup>33-36</sup> in amounts comparable with those found in hydatidiform mole and chorionepithelioma,<sup>13</sup> it is somewhat surprising that in normal pregnancy similar changes do not occur frequently. However, the fact

\*These comments are not intended to give a comprehensive review of the field and many citations have been omitted for brevity.

that in normal pregnancy the high gonadotropin level is maintained for a relatively short period may account in part for the difference. On the other hand, one might speculate concerning the high incidence of corpus luteum cysts in early pregnancy when the gonadotropin level is high.

What effect pregnancy or the hormones associated with pregnancy may have on tumors which are not known to arise from recognizable ovarian structures is largely a matter of surmise. Since the tumors are usually considered a complication of pregnancy and removed, the effect of pregnancy on their development cannot be observed over a period of time. Although it seems that the incidence of the various types may differ somewhat from that found among nonpregnant patients, it is difficult to determine definitely the age of the tumor. The high incidence of ovarian tumors occurring with the first pregnancy may possibly have some relation to the pregnancy but may merely mean that the tumors are discovered in the course of routine ante-partum examinations.

In general, the amount of estrogen in the cyst fluid was about that found in the cysts of nonpregnant patients.<sup>2</sup> This may be because the tumors were usually removed in early pregnancy when the estrogen level is low. Cysts removed post partum seemed to show more hormone. The findings would indicate also that the tumors do not store appreciable amounts of estrogen. However, two of the four dermoids removed early in pregnancy contained estrogen. This series is too small to permit very definite deductions.

### Summary

Thirty cases of ovarian cysts associated with pregnancy have been investigated and the findings compared with those of a series of nonpregnant patients previously reported.

Excluding 4 dermoid cysts the incidence of the various types of cysts was: follicle, none; corpus luteum, 7 (26.9 per cent); simple serous, 6 (23.1 per cent); papillary serous 2 (7.7 per cent); pseudomucinous 11 (42.3 per cent). Although the group is too small to make definite deductions, the incidence of corpus luteum and pseudomucinous cysts seems higher than in the series of nonpregnant patients.

Twenty and eight-tenths per cent of the ovarian cysts (30 of 144) of the entire series were associated with pregnancy. Sixty-six and seven-tenths per cent of the cysts (96 of 144) were from patients with history of one or more pregnancies. Of these 40.6 per cent (39 of 96) were primiparas and the cyst was associated with the pregnancy in 56.4 per cent of the cases (22 of 39). Seventy-three and three-tenths per cent of the cysts (22 of 30) associated with pregnancy were associated with the first pregnancy.

Twenty-seven and eight-tenths per cent and 28.5 per cent of the cysts occurred in patients in the age groups 15 to 24 and 25 to 34 years, respectively. In these groups, 35.0 per cent and 34.1 per cent of the cysts, re-



spectively, were associated with pregnancy. Of the cysts removed in the decade 15 to 24 years 30.8 per cent (8 of 26 cysts) from nonpregnant patients, 50 per cent (5 of 10 cysts) from pregnant patients and 50 per cent (2 of 4 cysts) from post-partum patients contained estrogen. In the cysts from patients in the age group 25 to 34 years, estrogen was found in 40.7 per cent of the cysts (11 of 27) from nonpregnant patients, 36.4 per cent (4 of 11 cysts) from pregnant patients and 66.7 per cent (2 of 3 cysts) from post-partum patients.

Of the cysts removed during pregnancy the percentages of the various types which contained estrogen were: follicle (no cysts); corpus luteum, 71.4 per cent (5 of 7 cysts); simple serous, 25 per cent (1 of 4 cysts); papillary serous, one negative; pseudomucinous, 14.3 per cent (1 of 7 cysts); dermoid 50 per cent (2 of 4 cysts). Of the 7 cysts removed post partum, there were no follicle or corpus luteum cysts; 2 simple serous, 1 papillary serous and 1 of 4 pseudomucinous cysts contained estrogen. Forty-three and three-tenths per cent of all the cysts associated with pregnancy contained estrogen in contrast to 33.3 per cent in the non-pregnant group. Excluding follicle and corpus luteum cysts from each series, the percentages which contain estrogen were 34.8 per cent to 22.1 per cent, respectively.

Gonadotropin was found in the fluids of ovarian cysts associated with pregnancy.

Three parovarian cysts, 1 cystic fibroid and 1 cyst of Gartner's duct associated with pregnancy were studied.

We wish to express our appreciation to the members of the staff for their cooperation in supplying the clinical material.

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Ramos, A. P., Albertelli, J. F., and Colombo, E.: *The Value of Quantitative Determination of Gonadotropin in the Diagnosis of Chorionepithelioma*, *Rev. argent. de cien. med.* 1: 8, 1943.

The authors state that the maximum guarantees of early diagnosis of chorionepithelioma are to be found through biologic tests. Since this neoplasm always secretes huge amounts of choriogonadotropins, the quantitative determination of these by-products, in the absence of pregnancy, is of utmost diagnostic importance. For diagnosis the presence of at least 50,000 rat units per liter are required.

The authors conclude that the existence of large amounts of gonadotropin is not essential if re-examinations of urine reveal an ascending curve following an abortion caused by a mole, or if a degeneration of the trophoblast is suspected. They carry out weekly estimates for at least two months, searching for 200 units. If this quantitative determination increases gradually to 500 or 1,000 units per liter the diagnosis can be established and treatment be instituted.

Two outstanding cases which were followed by hysterectomy and pathologic substantiation of the tumor are mentioned in this article.

CLAIR E. FOLSOME.

Matters, R. F.: *Sulphonamides and Purulent Peritonitis*, *M. J. Australia* 2: 85, 1943.

The author found that intraperitoneal sulfanilamide has proved most effective in cases in which the peritoneum has been infected. It is rapidly absorbed from the peritoneum within 24 hours. The gross pus must be removed before the powdered sulfanilamide is applied. The sulfanilamide does not appear to affect the healing of wounds or the normal state of the intestines.

WILLIAM BERMAN.

## ENDOMETRIOSIS AND PREGNANCY

### With a Report of Two Cases

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RECENTLY two cases of endometrial cysts complicating pregnancy were operated upon in this hospital. A review of the varied forms in which endometrial cysts may complicate pregnancy or be complicated by pregnancy has been stimulated by the rarity of this disease as an obstetric problem, and also, by its apparent increase in incidence.

It is not the purpose of this paper to review the subject of endometriosis. A study of the classic work of Sampson<sup>1-5</sup> and the more recent papers (Novak,<sup>9</sup> Keene and Kimbrough,<sup>10</sup> Payne,<sup>11</sup> Counseller,<sup>12</sup> Fallas and Rosenblum,<sup>13</sup> Dannreuther,<sup>14</sup> Meigs,<sup>15</sup> Holmes,<sup>16</sup> Haydon,<sup>17</sup> Jenkinson and Brown,<sup>18</sup> and others) will reveal the vast amount of research and the tremendous interest that this disorder has aroused.

The diagnosis of endometriosis is definitely on the increase, a fact which has impressed practically all recent workers in this field, many of whom give statistics as proof.

Sampson found that in 1925, 29.5 per cent of his laparotomies, 98 out of 332, showed endometriosis (quoted by Meigs<sup>15</sup>). Fallas and Rosenblum<sup>13</sup> report the lowest percentage—1.62 per cent endometriosis in 15,975 gynecologic laparotomies done in two Los Angeles private hospitals from May, 1930 to April, 1939. Holmes<sup>16</sup> had 80 proved cases of external endometriosis in 307 gynecologic laparotomies, an incidence of 26.0 per cent. The statistics given by Meigs<sup>15</sup> in 1941 are particularly revealing. In 400 private abdominal cases, 36 per cent were considered to have endometriosis grossly, and 28 per cent showed endometriosis microscopically. This contrasts with 8.3 per cent by gross diagnosis and 5.8 per cent by microscopic diagnosis in 400 Massachusetts General Hospital ward abdominal cases.

This is statistical evidence for two important facts peculiar to endometriosis. It is definitely a social-economic disease, raining its pelvic devastation, for some unexplained reason, much more frequently upon the higher social and economic strata of womanhood. The second fact that Meigs' statistics bear out is the importance of careful gross diagnosis, because microscopic studies, necessarily somewhat incomplete, often fail to show definitely, endometriosis.

All authors are agreed that the greatest incidence of endometriosis is found in the last half of the fourth decade of life, a period of reduced fertility which is still in the childbearing age. A review of the reported cases of endometriosis and pregnancy reveals a high incidence of elderly primiparas. Internal endometriosis (adenomyosis and adeno-

myoma) is found more frequently in the early forties; it is not as commonly associated with sterility as is external endometriosis.

Combining a discussion of endometriosis and pregnancy is in some measure a paradox. Reynolds and Macomber<sup>19</sup> give 88 per cent as the normal fertility in marriage. This contrasts with the much reduced fertility in cases of endometriosis. Counseller<sup>12</sup> found that 48.9 per cent of 131 married patients with the disease had either never been pregnant, or had only miscarriages or abortions, so that the absolute sterility rate was 32.1 per cent. Payne's<sup>11</sup> series showed that 40 per cent of 238 married patients with endometriosis had never been pregnant. Haydon<sup>17</sup> reported a relative sterility rate of 53 per cent. Keene and Kimbrough<sup>10</sup> found absolute sterility in 40.9 per cent of 118 cases, and in the remaining cases 9.5 years had elapsed since the birth of the last child. Jenkinson and Brown<sup>18</sup> stated that 34 per cent of their patients complained of absolute sterility. Many explanations have been offered for this relative and absolute sterility. Associated pathologic lesions of the female genitalia are very frequent, and this associated lesion may often be the indication for operation. Combining Counseller's<sup>12</sup> and Masson's<sup>20</sup> series, 54.5 per cent of 844 cases of internal and external endometriosis revealed associated pelvic disorders. These disorders include myomas, endometrial hyperplasia, chronic pelvic inflammatory disease, ovarian cysts (exclusive of endometrial cysts), solid tumors of the ovary, and other disorders. These pathologic processes are all well known to be causative and contributing factors to both absolute and relative sterility. Pelvic adhesions incident to endometriosis must certainly be a factor. The most logical reason for these adhesions being a sterility factor would seem to be tubal occlusion, yet in 293 cases of endometriosis Sampson<sup>6</sup> found both tubes patent in 284 cases, a strong point in his retrograde menstruation theory. A possible explanation is that adhesions about the ovary prevent the ovum from escaping or prevent it from entering the tubal lumen. A factor not sufficiently stressed in previous publications is the diminished frequency of coitus in these cases with endometriosis. Coitus is diminished because of the complaint which brings them to the physician, namely dyspareunia, metrorrhagia, menorrhagia and similar complaints.

Meigs<sup>15</sup> approaches the subject of sterility and endometriosis from a different angle. He believes that delayed marriage, lack of early and interrupted childbearing, and the consequent persistent and uninterrupted menstrual cycle, are conducive to the development of endometriosis, particularly in the higher social and economic levels where delayed childbearing and endometriosis are most common.

Because pregnancy is frequent enough following conservative operative procedures, where conservatism is possible in endometriosis, the surgeon must always bear in mind the importance of preserving the childbearing function in these relatively sterile women. This need for conservatism calls for the finest judgment at the operating table, and no rules can be made which are applicable to all cases. The general principle only can be stated: if the disease is not too extensive and the patient is anxious to become pregnant, conservative surgery should be practiced, with the full understanding that a subsequent operation may be necessary, and that the odds for a pregnancy are long.

The surgeon must consider in what ways endometriosis may complicate pregnancy, as must the obstetrician in his differential diagnosis of obstetric problems. The two cases to be reported, and a review of the literature, prove the fallacy of Sampson's statement<sup>2</sup>: "Should a patient with this lesion become pregnant and the latter condition recognized, there would not be sufficient indications present to justify an abdominal operation." Undoubtedly many patients with asymptomatic endometriosis, minimal or moderately extensive, have uncomplicated ante-partum, intrapartum, and post-partum courses. Sampson's belief<sup>4</sup> that pregnancy's influence on the endometriosis implants "lessens their incidence and the subsequent involutionary changes may possibly retard the future development, or even cause the regression, of any implants present," may well be true, but it is difficult of statistical proof.

### Ectopic Decidual Reaction and Pregnancy

This subject has been very thoroughly studied, and the literature is replete with articles discussing the various anatomical sites, the incidence, and the significance of ectopic decidual formation.

Walker<sup>21</sup> in 1887 was the first to describe decidua beneath the serosal epithelium of the pelvic peritoneum in a case of intra-abdominal pregnancy. Hirschberg<sup>22</sup> in 1905, Taussig<sup>23</sup> in 1906, Hofbauer<sup>24</sup> in 1929, and Weller<sup>25</sup> in 1935, reviewed the subject, and they have cited instances of reported occurrence in the pelvic peritoneum, ovaries, tubes, appendix and other portions of the intestines, omentum, diaphragm, splenic capsule, and other intra-abdominal tissues, as well as in pelvic lymph nodes, cervix, vagina, and abdominal scars. Reported cases of decidual reaction in the cervix have often been associated, for some unknown reason, with placenta previa. Geipel<sup>26-28</sup> did much work on this subject and reported many instances of its occurrence in the diaphragm (peritoneal surface), splenic capsule, and pelvic lymph nodes. He believed that the peritoneal transudate in pregnancy contained certain substances or hormones capable of producing this response. Taussig's<sup>23</sup> interesting theory was that the placental metabolic products escaped out of the tubes and incited the production of decidua.

As Weller<sup>25</sup> pointed out, the sites of election for ectopic decidua correspond impressively with the regions where endometriosis is most commonly found. Endometriosis and ectopic decidua formation decrease as the distance from the ovaries increases. Ectopic decidua formation on the ovaries varies from 40 per cent to 100 per cent in the cases where ovaries were examined microscopically during or immediately after a pregnancy. Harbitz<sup>29</sup> found ectopic decidua formation on the ovaries in all seven of his cases. Hofbauer<sup>24</sup> found decidual reaction on the posterior uterine surface in 15 of 23 pregnant uteri which he examined. The fact that the cellular elements immediately beneath the serosal cells may be stimulated by pregnancy to form decidual cells, and the fact that, as the distance from the ovaries increases the incidence diminishes, add weight to the Iwanhoff-Meyer serosal (ectomic) heteroplasia theory of endometriosis. Olson and Hansmann<sup>30</sup> believe that the finding of ectopic decidua in the areas noted is more in accord with the Halban lymphatic-spread theory of endometriosis.

Every obstetrician and gynecologist is familiar with the gross picture of ectopic decidua at operation. The ovaries particularly present a very striking gross abnormality. Early in pregnancy there are superficial, slightly raised sheets which are reddish-white, wrinkled and velvety or there are lentil-sized nodules or flecks over the ovarian surface. Later in pregnancy these surface areas become more granular and whitish, suggestive of wax drippings. If more complete sectioning of pathologic tissue were done, ectopic decidual formation would probably be found in every pregnant case.

Ectopic decidua formation does not signify endometriosis, for endometrial glands must in addition be identified in order to apply this term properly. Most of the cases of endometriosis associated with pregnancy describe stromal decidual reaction in the microscopic studies. Those reports of ectopic decidual formation without pregnancy are probably the pseudodecidua of the late premenstrual phase.<sup>31, 32</sup>

### Endometriosis and Pregnancy

According to Cullen,<sup>33</sup> "adenomyomas" containing uterine mucosa are found in the body of the uterus, rectovaginal septum, uterine horn or tube, round ligament, ovary, uterosacral ligament, sigmoid flexure, rectus muscle, and umbilicus. Other reports have added the rectum, cecum, appendix, small intestines, retroperitoneal and inguinal lymph nodes, bladder, cervix and vagina, laparotomy scars, inguinal hernia sac or patent canal of Nuck, and even the lung. It has been the custom to divide endometriosis into the internal and external types. The internal type includes only the type limited to the uterine musculature, more commonly termed uterine adenomyoma or adenomyosis, and the external type includes all other areas containing ectopic endometrial tissue. Fallas and Rosenblum<sup>13</sup> in 260 cases of endometriosis found the internal type alone in 49.6 per cent (129), external alone in 36.5 per cent (95), and combined in 13.9 per cent (36). Masson<sup>34</sup> in 576 endometriosis cases found adenomyoma of the uterus in 81.9 per cent (482), ovarian endometriosis in 13.4 per cent (77), rectovaginal in 3.5 per cent (20), and sigmoid in 2.4 per cent (14). Haydon<sup>17</sup> in 569 cases of endometriosis found it in the ovaries in 60.6 per cent (345), uterus 55 per cent (313), cul-de-sac 33.5 per cent (191), ligaments of the uterus 12.1 per cent (69), tube 2.8 per cent (16), rectum 2.4 per cent (14), and the sigmoid, abdomen, bladder and appendix in smaller percentages. Adenomyoma or adenomyosis of the uterus is less often associated with the sterility factor, a prominent feature of cases with external endometriosis.

### Internal Endometriosis (Uterine Adenomyoma or Adenomyosis)

Many of the reported cases of internal endometriosis and pregnancy represent incidental pathologic findings, and the reasons for removal of the uterus are not exactly clear, particularly in the German literature.

Amos<sup>35</sup> in 1905 reported a case of adenomyoma of the uterus with decidual reaction, a supravaginal hysterectomy being done at the time of a 5 months' intrauterine pregnancy. Robert Meyer<sup>36</sup> in the same

year described three cases of adenomyoma and pregnancy, one with decidual reaction. Sampson<sup>cited by 37</sup> reported a case with a myomatous nodule on the posterior wall of the uterus which pathologically was proved to be adenomyoma with decidual reaction. Cullen<sup>38</sup> wrote of an adenomyoma of the right uterine horn; the adenomyoma showed decidual reaction and was associated with subserous and intramural myomas and an unruptured tubal pregnancy on the left side. Aschheim,<sup>39-41</sup> in 1923 and 1929, in three separate papers, had three cases of adenomyoma with pregnancy and decidual reaction, one being associated with an endometrial cyst of the right ovary and endometriosis of the right uterosaeral ligament. The reason for laparotomy in the above cases was usually the clinical diagnosis of a myomatous uterus. The additional diagnosis of an unruptured tubal pregnancy was made in Cullen's case. It is possible that the uterine asymmetry and pregnancy could be interpreted preoperatively as a cornual pregnancy, but there are no such cases in this group.

Uterine rupture is probably the most dramatic of complications of adenomyoma of the uterus and pregnancy. A wall weakened by islands of endometrial stroma and possibly more deeply invaded by the chorionic villi, can account for uterine rupture as well as uterine atony.

Schäfer<sup>42</sup> in 1918 reported a 41-year-old, para x, 7 months pregnant with twins, who upon lifting a heavy object ruptured her uterus and lost three liters of blood into the peritoneal cavity. A 10 cm. uterine rupture was found, and this area of rupture showed, microscopically, adenomyoma and decidual reaction. Richardson<sup>43</sup> in 1919 published a pathologic report of a case of spontaneous rupture of the uterus at the anterosuperior surface which showed decidual cells extending deep into the musculature at the site of rupture. Aschheim<sup>40</sup> cited a case of peritonitis following the performance of a criminal abortion in which the removed uterus did not show the actual perforation, but there were scattered areas of endometrial glands and stroma with decidual reaction deep in the uterine musculature. Schlugt<sup>44</sup> in 1926 reviewed the causes of uterine rupture and described a case of a 32-year-old, para v, whose uterus he ruptured posteriorly for a length of 4½ cm. at the time of a digital completion of a 4 months' abortion. A hysterectomy was done, and at the region of the tear endometriosis was found. In addition, the original abortion had been criminal; the uterus had been perforated by an instrument at this same area, and the omentum was healing over the perforated area. Spontaneous rupture at the onset of labor was the complication of Stone's<sup>45</sup> case. At laparotomy a posterior uterine rent, 5 cm. long, was found, and the abdomen contained one liter of bloody fluid. Adenomyosis with decidual reaction was found around the area of rupture and elsewhere in the uterus.

Uterine atony due, supposedly, to internal endometriosis has been infrequently reported. Schweitzer<sup>46</sup> at the time of section for placenta previa found a tumor nodule on the posterior surface of the uterus, adherent to the sigmoid and obliterating the cul-de-sac of Douglas. A hysterectomy was done because of uterine atony (a not uncommon added complication of placenta previa), and the tumor was found to be an adenomyoma with decidual reaction. Szene's<sup>47</sup> post-partum hemorrhage case after a normal delivery was followed by a vaginal hysterectomy. The pathologic finding was adenomyosis and decidual reaction one-third of the distance through the uterine wall at the placental

site. Sackett<sup>48</sup> explained the uterine atony at a second cesarean section necessitating hysterectomy upon a large number of endometrial islands with decidual reaction, in the myometrium.

An adenomyoma in the lower uterine segment could easily be interpreted clinically as a myoma, and a section performed because of suspected or evident dystocia. Lochrane<sup>49</sup> did a section on a 42-year-old primipara because of a tumor the size of a tennis ball on the posterior uterine wall and because of a breech presentation. The tumor was an adenomyoma with decidual reaction. Josselin de Jong and de Snoo<sup>50</sup> described a tumor filling the cul-de-sac of Douglas, grossly suspected of being a sarcoma, in a 39-year-old, para i, patient. The section was done because of the danger of uterine rupture. The tumor was removed, found to be an endometrial tumor which had "grown-into" the uterine musculature, but no connection could be found with the endometrium. Ectopic decidual reaction was found, in addition to its presence in the tumor mass, in both ovaries, both broad ligaments, the left round ligament, and the right tube. It is not altogether clear from the report whether this should be considered an adenomyoma of the uterus or a cul-de-sac endometriosis. Schweitzer's<sup>46</sup> case mentioned above could very likely have had serious dystocia from the tumor nodule on the posterior surface of the uterus, had it not been complicated by a placenta previa and had vaginal delivery been attempted. In addition to Schweitzer's report of adenomyoma and placenta previa, J. Whitridge Williams<sup>51</sup> reported a case in 1904 which died when 6 months pregnant from a central placenta previa. Autopsy showed extensive adenomyosis with decidual reaction in both the anterior and the posterior uterine walls.

Sampson's<sup>7</sup> case of ectopic pregnancy was quite unusual. His patient had had a ventrofixation of the uterus and an attempted tubal sterilization, subsequent to which she developed an ectopic pregnancy in an area of endometriosis at the left uterine cornu.

The statement has been glibly made that abortions and miscarriages may be due to uterine adenomyosis or adenomyoma. Any uterine lesion may increase the incidence of abortions, but statistical proof of the role played by internal endometriosis is wanting.

In twelve of the above cases the age is available. The average age was found to be 36.1 years. In ten of the cases the parity was given. Four were primigravidas, two para i, and one each were para ii, iii, v, and x respectively.

### External Endometriosis and Pregnancy

External endometriosis, as previously defined, includes all cases of endometriosis exclusive of those involving the uterine musculature from within. A classification of such endometriosis cannot be exact, for in many instances the lesions overlap from one area into another. For example, posterior cul-de-sac endometriosis may be a part of, or in stages become, endometriosis of the rectovaginal septum and vaginal endometriosis. External endometriosis may be found on the pelvic peritoneal surfaces, the uterine ligaments, ovaries, tubes rectovaginal septum, vagina, cervix, intestines (appendix, small and large intestines),



hernial sacs, umbilicus, abdominal scars, vulva, pelvic lymph nodes, and even lungs.

In reviewing the cases of endometriosis and pregnancy many examples of the posterior cul-de-sac or rectovaginal septum and the ovarian groups are found, but in the other groups only an occasional, isolated report is found. This is in accord with what would be expected from consideration of the relative frequency with which endometriosis is found in the various areas, and in accord with the pathologic picture most liable to produce symptoms if complicated by pregnancy.

Eleven cases of posterior cul-de-sac or rectovaginal septum endometriosis and pregnancy were found in the literature. Many of these reports were sketchy and were reported before delivery of the pregnancy which was under consideration. Griffith<sup>52</sup> in 1913 was the first to report a case. His case was a 37-year-old patient with one previous pregnancy who, when examined at 5 to 6 months of a gestation, was found to have a cervix fixed by an ill-defined mass between it and the rectum. Biopsy of the vagina over this mass, taken in an area of soft and spongy tissue which bled easily upon trauma, showed endometriosis with decidual reaction. The lesion increased in size over the following month; radium was applied, and by one month from term the mass was much smaller and probably offered no dystocia to vaginal delivery. Lochrane<sup>53</sup> in 1922, described finding an irregular nodule imbedded in the posterior vaginal fornix of a 33-year-old primigravida, 18 to 20 weeks pregnant, who had had bowel bleeding. A biopsy at this time and eight weeks later was reported as adenomyoma with decidual reaction. Ulesko-Stroganowa<sup>54</sup> encountered a lentile-sized rectovaginal tumor, causing bleeding from the rectum, in a patient ten weeks pregnant; adenomyoma with decidual reaction showed microscopically. The subsequent course of this patient was not given. Josselin de Jong and de Snoo's<sup>55</sup> case in 1925, aged 39 and para i, was sectioned because of an abnormal presentation and the finding of a tumor mass behind the vaginal vault. The growth posterior to the uterus was thought at operation to be a sarcoma and was surgically removed, only to find on examination, endometriosis with extensive pelvic decidual reaction. The mass was stated to have invaded the uterus, but from description it seemed most likely to have been of cul-de-sac origin. Haselhorst<sup>55</sup> in 1933 excised a small nodule from the posterior cul-de-sac of a 27-year-old patient and diagnosed by the decidual reaction in an area of endometriosis, a very early pregnancy. Otto von Franqué<sup>56</sup> reported in 1934 two cases of endometriosis and pregnancy. The first case was a 39-year-old, para ii, who three years prior to delivery had a walnut-sized nodule between the rectum and the cervix, proved by biopsy to be endometriosis. She was delivered of a 3,620 Gm. fetus by difficult forceps and Dührssen's incisions. Von Franqué did not feel that the difficult delivery was related to the nodule, because the nodule had become smaller than walnut-size early in pregnancy.

Szymanowicz's<sup>57</sup> patient, 41 years old, had a tumor which was finger-size between the cervix and the rectum, producing postcoital bleeding and showing histologically endometriosis. She returned fourteen months later, at which time she was two months pregnant, and the tumor mass was smaller and continued to diminish in size as the gestation advanced.

She had a normal delivery and puerperium, and when examined one month after discharge, no tumor could be felt. Hay,<sup>58</sup> in 1939, reported the removal of a polypoid mass (2 by 1 in.) per vaginam, arising in the rectovaginal septum and causing dyspareunia and leucorrhea. She was 25 years old, had been married for 6 months, and at the time of removal was overdue for her menstrual period. The mass had doubled in size in the two weeks before removal. Pathologically, the tumor was endometriosis with decidual reaction. The mass again grew to its original size during the ensuing month, and at about the sixteenth week of the gestation began to recede in size. At a later interval in the pregnancy it was the size of a fifty-cent piece and 1 cm. thick. She was sectioned electively, and at operation no cul-de-sac endometriosis was found. Twelve days postoperatively the vaginal lesion was biopsied, again revealing endometriosis, but no decidual reaction. Four months following delivery she was again pregnant, and the area of endometriosis, as previously, grew larger and later began to recede. In the eighth month of this gestation she was again sectioned, this time because of a twin pregnancy. Five months after this operation, several shotty nodules were found in the rectovaginal septum which showed the same histologic picture of endometriosis. This case is a striking contradiction to the statistics showing a high absolute and relative sterility rate in endometriosis, for here we have a 27-year-old female who has been married for less than two years, with three children, all under one year of age.

Batzfalvy,<sup>37</sup> in a review of the subject, described his case of a 26-year-old female who had rectovaginal endometriosis, proved by biopsy. She was irradiated, and a temporary amenorrhea resulted. She then became pregnant, and the lesion increased in size, and ulcerated. A section-hysterectomy was done one month from term. The ovaries were conserved at the operation, and a follow-up history revealed that she had vaginal bleeding regularly every month, in addition to postcoital metrorrhagia.

Portes, François, and Varangot,<sup>59</sup> and later Portes and Varangot<sup>60</sup> in a review of endometriosis and pregnancy, reported a patient who was 32 years old and who had had one miscarriage. She began to notice vaginal bleeding in the seventh month of her second pregnancy. Upon examination an ulcerating tumor mass was found extending into the vagina from the posterior cul-de-sac. The mass was the size of a large "nut." A biopsy of the tumor mass was reported as "spinal cell epithelioma of the vagina." The patient was delivered by section-hysterectomy, and four days post partum a biopsy of the vaginal tumor showed endometriosis. Vignes,<sup>61</sup> in a discussion of the above case, cited a 28-year-old multipara, who had a rectovaginal endometriosis and whose pregnancy terminated with an abortion at 22 weeks. The nodule was later excised, returned in two months, and the recurrence was irradiated. Sixteen months after the application of radium she delivered a 30 weeks premature infant. Two months after this delivery the rectovaginal septum was hard, but no definite tumor mass could be felt, despite the fact that four days post partum an egg-sized, tender mass was felt in this region.

The second most frequent site for endometriosis complicating pregnancy is in the ovary. It is in this group that the two new cases reported in this paper belong. Ovarian endometriosis is much more common than cul-de-sac endometriosis, yet case reports of ovarian endome-

triosis complicating pregnancy are relatively rare. The difficulties of accurate palpation of the ovaries in the presence of an intrauterine pregnancy may account for some of the scarcity of reported cases. All too frequently cursory pelvic examination (or even no pelvic examination!) of prenatal patients is done, and many endometriosis cases are missed or the findings interpreted as salpingitis. Many small endometrial cysts are followed throughout pregnancy, cause no complications, and the association is never realized.

Sampson<sup>2-3</sup> in 1922 reported the first case of pregnancy and ovarian endometriosis. His patient was 37 years old and had never previously been pregnant. A laparotomy was done for a myomatous uterus, and at operation a cyst, 2 cm. in diameter, filled with chocolate material, was found in the left ovary. Decidual reaction was found in the lining of this cyst, as well as in an endometrial implant on the posterior uterine surface. The uterus contained a fetus, 14 mm. long.

Winestine<sup>62</sup> in 1924 described a patient, 35 years old, who had an oophorocystectomy performed in early pregnancy because of left lower quadrant abdominal pains, chills, and fever. An endometrial cyst, the size of a hen's egg, showing decidual reaction in the wall, was found in the left ovary. There is no very satisfactory explanation in this case report of the patient's presenting complaints. Aschheim's<sup>41</sup> case in 1929 of a right ovarian endometrial cyst was described under internal endometriosis, for the ovarian cyst was an incidental finding.

Shaanning<sup>63</sup> in 1930 reported an adherent endometrial cyst of one ovary removed from a 29-year-old patient, sixteen to eighteen weeks pregnant. Von Franqué,<sup>56</sup> in addition to the cul-de-sac endometriosis case, in 1934 described a fist-sized ovarian endometrial cyst which had been removed from a 28-year-old patient five to six weeks pregnant. At operation von Franqué's case showed cul-de-sac thickening. The patient's presenting complaint was leucorrhea, and she aborted the pregnancy on the thirty-eighth postoperative day.

Ramos<sup>64</sup> in 1940 detailed a patient, 27 years old, who had had the second criminal abortion. Because of continued vaginal bleeding a laparotomy was done, and an egg-sized cyst was removed from the right adnexal region, and a nut-sized cyst was resected from the left ovary. The right ovarian cyst was definitely endometrial, but the left adnexal mass was not described microscopically. McKenzie<sup>65</sup> in 1943 had an interesting patient, 25 years old, who showed, in the same ovary, endometriosis and a ruptured ovarian pregnancy. This patient, from the operative description, also had cul-de-sac endometriosis.

Although ovarian cysts of endometrial origin have been termed "perforating, chocolate cysts" by Sampson, it is strange that so few cases of severe and sudden rupture of these cysts and a resulting "surgical abdomen" are reported. The cyclic hemorrhage and increased intracystic pressure would seem to offer good potentialities for such an accident. The usual process seems to be an occasional leak with rapid walling-off by reactive inflammation, and later, extensive adhesions. A laparotomy is rarely performed as the symptoms are usually of transient duration and are seldom sufficiently severe. It is usually the persisting

discomfort and other symptoms of endometriosis which bring the patient to the surgeon.

Novak<sup>9</sup> in 1931 reported 3 cases of his own who were found to have had endometrial cysts which spontaneously ruptured. The preoperative diagnosis in two cases was acute appendicitis, and in the other, ovarian cyst with twisted pedicle. Novak was able to find only one similar case in the literature, a case recorded by Lee,<sup>66</sup> which was not accompanied by microscopic confirmation of its endometrial origin.

Because of the lack of cyclic hemorrhage into the cyst, leakage and frank rupture of an endometrial cyst would seem less common during pregnancy. Unusual pressure, and the break-up of adhesions by an enlarging uterus, are factors that might lead to such leakage and rupture. Spontaneous rupture of an endometrial cyst in the third trimester of pregnancy was the first of the two cases encountered in this hospital. The second case, a large ovarian cyst in the first trimester of pregnancy, represented an endometrial cyst with evidence of leakage, but no definite rupture.

### Case Reports

CASE 1.—(History number 161381, Gyn. Pathology number 56338). This was a 25-year-old white female who registered in the obstetrical dispensary on August 17, 1942. She stated that her last menstrual period was June 6, 1942, making her due by dates for this delivery on March 13, 1943. She had been married six years, no contraception had been used, and she had been unable to become pregnant. At the time of her dispensary visit and also postoperatively, she denied abnormal vaginal bleeding and dysmenorrhea. Physical examination and laboratory studies were not revealing except for the pelvic examination. The uterus was found to be enlarged to about the size of a three months' pregnancy. On the anterior surface of the uterus was a firm, subserous nodule, about 2 cm. in diameter. In the region of the left ovary was a 4 to 5 cm. adherent, firmly cystic mass. The right ovary was thought to have been felt and was thought to be normal. The impression, in addition to the intrauterine pregnancy, was a small myoma of the uterus and ovarian cyst, left. Because of the lack of symptoms and the long period of sterility, it was considered advisable to follow the patient carefully and institute any necessary treatment later.

She was checked at frequent intervals in the out-patient department, and the antenatal course, until the episode demanding admission, was essentially uneventful, except for a transient right lower quadrant pain on October 28, 1942, unaccompanied by abdominal tenderness or tenderness on rectal or pelvic examination.

On February 9, 1943, she reported to the accident room, stating that about 8 hours previously she had been seized with a sudden, severe, sharp, and nonradiating right lower abdominal pain. The onset of this pain was while straining at stool; she had been constipated for three days. The pain continued and was accompanied by slight nausea, but no vomiting and no urinary symptoms. On examination there was an estimated 2,000 Gm. fetus in right occipito-anterior, vertex floating, and fetal heart regular in the right lower quadrant. There was no muscle

spasm or rigidity in the abdomen, but there was tenderness in the right lower quadrant of the abdomen extending from a level with the umbilicus almost to Poupart's ligament. Rebound tenderness and motion of the uterus referred pain to the right lower quadrant. The previously diagnosed myoma and ovarian cyst were not felt, and by rectal examination the cervix was long and closed and there was slight tenderness high on the right. The temperature was 99° F., and white blood count was 17,000. The other laboratory studies were within normal limits.

She was observed for sixteen hours without any particular change in her condition. The white blood count taken at intervals varied between 14,400 and 18,500 and the temperature was never above 99.2° F. The following possibilities were entertained: (1) Twisted ovarian cyst, (2) acute appendicitis, and (3) degenerated myoma. Because appendicitis could not be ruled out an immediate exploratory operation was decided upon. Under gas-oxygen-ether anesthesia a McBurney incision was made. Immediately upon entering the peritoneal cavity a moderate amount of brownish-black, semisolid material was encountered. The right ovary was felt as an elongated, raised area firmly attached to the posterior surface of the uterus, and the ovarian surface was made irregular by firm, small, tubercle-like granules. An appendectomy was done, the McBurney incision closed, and a midline incision made. A classical cesarean section incision was made and a 2,280 Gm. female child in fair condition was extracted. On the lower portion of the anterior wall of the uterus was a 2.5 cm. myomatous nodule projecting subserously. The uterus was delivered. The right ovary was found to be elongated and flattened, adherent to the posterior surface of the lower uterine segment. The adherent tissue became very thin at the peripheral points of attachment of this ovary, and at one point adherent bands were nonexistent, and brownish-black substance was escaping.

This material was found in the cul-de-sac and disseminated far down on the right anterior portion of the abdomen. Loops of rectosigmoid were adherent in the posterior cul-de-sac. The left ovary was also adherent and elongated at a higher level on the uterus, its distal portion converted into a purplish cyst about 6 cm. in diameter (Fig. 1). This cyst was later found to be filled with chocolate material. Because of the extensiveness of the lesion, typically endometrial, it was decided that a bilateral salpingo-oophorectomy and subtotal hysterectomy was the procedure of choice. This was done. The patient received intravenous fluids, plasma, and blood during the operation and was returned to the ward in good condition.

She had an uneventful postoperative course. The temperature never rose about 100.2° F., and she was discharged on the fifteenth postoperative day. The baby was discharged on the twenty-fifth day with a weight of 2,580 Gm. At 6 weeks post partum, pelvic examination revealed the cervical stump well suspended with a slight induration to the left of the suspended stump. She has been followed in the gynecology dispensary with menopausal symptoms which have been successfully treated with stilbestrol and phenobarbital.

A complete pathologic study of the specimen revealed a post-section uterus, lined with decidua tissue. The small subserous nodule was a typical fibromyoma. There was an extensive decidua reaction over the posterior surface of the uterus (Fig. 4). Both the right and the left endometrial cysts were found to be lined with fragmented cuboidal

epithelium, beneath which there was a narrow zone showing endometrial stroma with irregular groups of decidual cells dispersed throughout this stroma, and numerous pigment-laden macrophages. The walls of the cysts peripheral to the endometrial tissue showed a narrow zone of ovarian stroma. These were noted grossly over the surface nodules which proved, microscopically, to be of decidual tissue, and which were of a much more fibrous character than the usual decidual tissue (Figs. 2 and 3). These nodules were found over the surface of both ovarian cysts. The tubes were normal and the appendix showed no lesions.

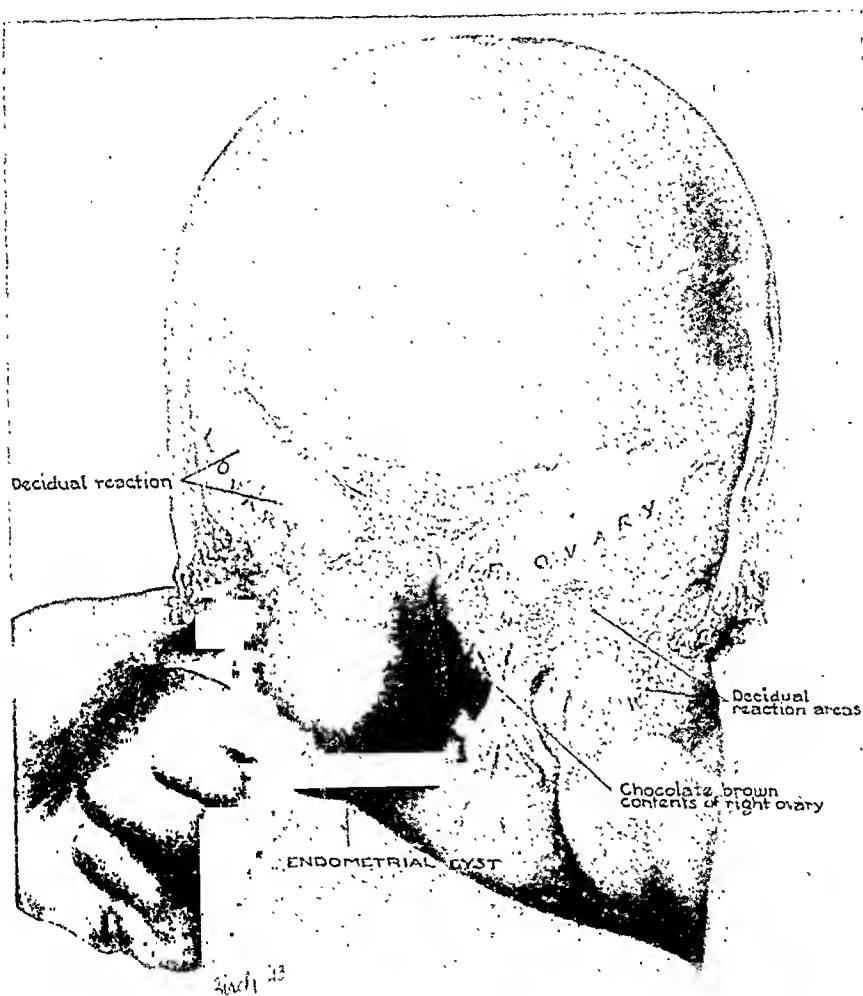


Fig. 1.—(Case 1.) A drawing of the gross specimen as viewed from the posterior aspect at the time of operation. The pregnant uterus and normal tubes are seen. The left ovary is elongated and adherent with the distal end converted into an endometrial cyst. The right ovary and ovarian cyst are firmly attached to the uterus, and the point of rupture is seen. The surface decidual reaction is shown over both ovaries, and there are intestinal adhesions posteriorly.

This was a 25-year-old primigravida who was known to have an ovarian cyst early in pregnancy. She underwent an exploratory laparotomy at 36 weeks because of severe right lower quadrant pain. A ruptured right endometrial cyst was found, and in addition there was a left endometrial cyst. A 2,280 Gm. female child which survived was delivered by cesarean section, and a subtotal hysterectomy, bilateral



Fig. 2.—A low power cross section of the right endometrial cyst wall in Case 1, showing on the left side the surface decidual reaction and on the right side of the section the internal cyst wall surface.

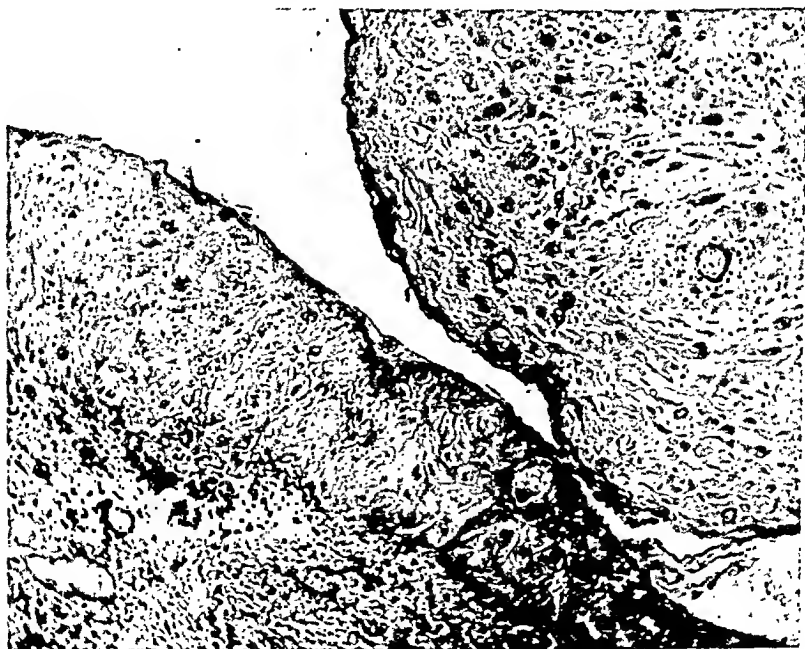


Fig. 3.—A high power study of the ovarian surface decidual reaction with nodules in Case 1.

salpingo-oophorocystectomy, and appendectomy were done. The patient made an uneventful recovery.

This patient had six years of sterility, but despite close questioning postoperatively she denied dysmenorrhea, abnormal uterine bleeding, lower abdominal pains or other symptoms commonly associated with endometriosis. A review of the operative findings (Fig. 1) reveals the probable cause of the rupture of this endometrial cyst: the cyst was adherent to the uterus and as the uterus enlarged with pregnancy the peripheral adherent areas of the cyst thinned out until they became separated, allowing contents of the cyst to escape.

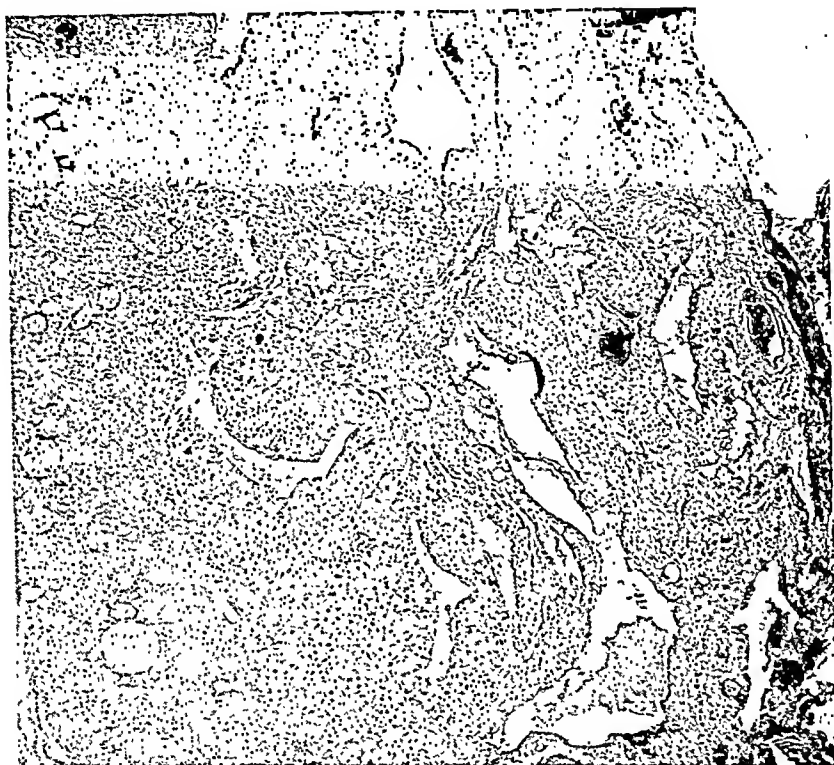


Fig. 4.—A section of the ragged, lower posterior uterine serosal surface in Case 1. The decidual reaction can be seen in one compact zone and also scattered in the adherent strands of tissue.

CASE 2.—(History number 285043, Gyn. Pathology number 56357.) This was a 23-year-old white female who was first seen by Dr. Richard TeLinde on February 2, 1943. She stated that her last menstrual period lasted for three days beginning November 22, 1942, and that this period was scant. For the month previous to being seen she had experienced some aching discomfort in both lower quadrants of the abdomen, with greater discomfort on the left side. She had been married two years and had used no type of contraception. The menstrual history had previously been quite normal, and she had had only minimal dysmenorrhea. There were no previous episodes of lower abdominal pain. This was her first pregnancy.

On examination there was a rounded, cystic mass filling up the right lower quadrant of the abdomen, and by pelvic examination this was thought to be an ovarian cyst, arising from the right ovary. The cervix



was soft, and the uterus was moderately enlarged and pushed to the left. The left ovary was not felt. There was a small Bartholin cyst on the right side. Laboratory studies were within normal limits. The impression was ovarian cyst, right, and pregnancy, intrauterine.

On February 12, 1943 under sodium pentothal-ether anesthesia a laparotomy was done. Upon opening the peritoneal cavity a cyst, about the size of a grapefruit, presented itself. This cyst replaced the right

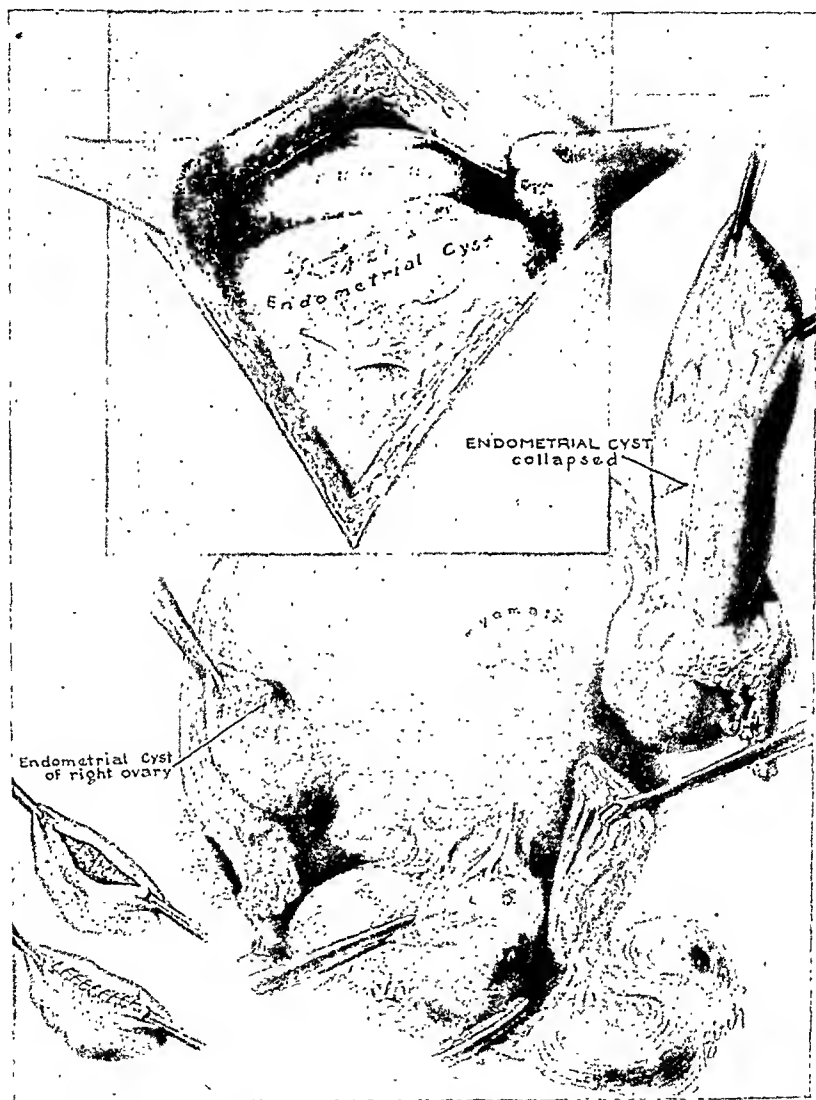


Fig. 5.—(Case 2.) At drawing at the operating table, showing the pregnant uterus, small subserous myomata, the large right endometrial cyst, and the small left endometrial cyst. The adherent intestines are represented with their small surface purplish reaction. A right salpingo-oophorectomy, resection of the cyst of the left ovary, and appendectomy were done.

ovary, was thick-walled and covered with shaggy adhesions, and was adherent to the posterior surface of the uterus and to the base of the broad ligament. There was a small amount of brownish, chocolate material scattered over the pelvis, and the serosa of the sigmoid colon, rectum, and appendix showed evidence of irritation presumably from this substance. The left ovary was about one and one-half times normal

size, and there was one dark, hemorrhagic area, about one em. in diameter, on its superior surface. The tubes were perfectly normal, and the uterine was softened and enlarged to the size of a 12 weeks' pregnancy. On the posterior surface of the uterus there was a subserous myomatous nodule about one em. in diameter (Fig. 5). A right salpingo-oophorectomy, resection of small cyst of the left ovary, and appendectomy were done. The large cyst was ruptured upon attempting to release it from its adhesions and about 300 to 400 c.c. of chocolate-colored material escaped.

Microscopically the large right ovarian cyst and the smaller cyst resected from the left ovary showed a poorly preserved lining of flattened epithelium, with, beneath this lining a narrow zone of endometrial stroma, many areas of which were converted into decidual tissue (Figs. 6, 7 and 8). There were numerous pigment-laden macrophages scattered through this same zone. The remaining portions of the walls of these cysts showed a few active, though compressed, ovarian elements.

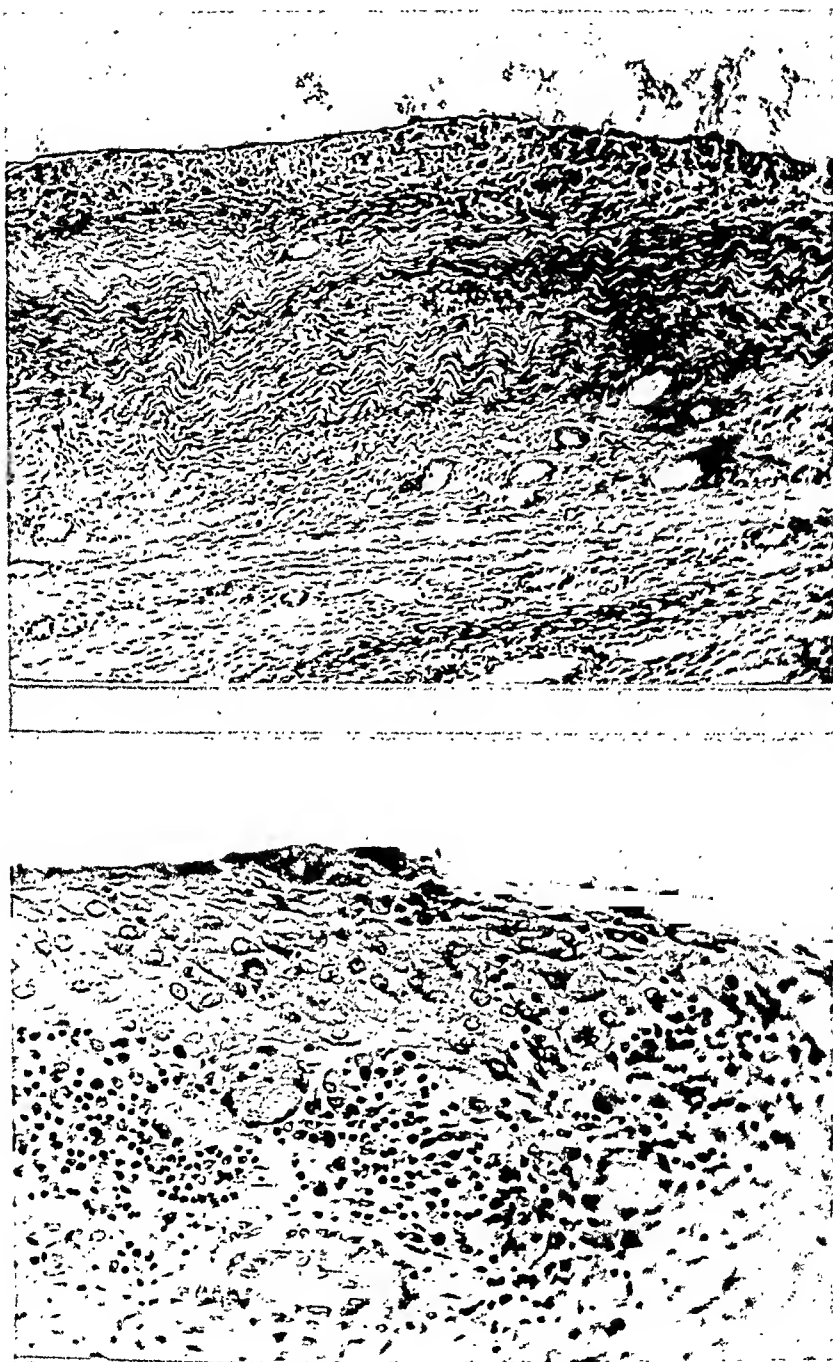


Fig. 6.—The inner surface of the right ovarian cyst in Case 2, showing the scattered decidual reaction and the cellular infiltration.

No decidual nodules were found on the surfaces of these cysts. The right tube was normal microscopically, as was the appendix.

The patient had an uneventful postoperative course and was discharged from the hospital on the seventeenth postoperative day. The corpus luteum of pregnancy was not recognized at operation and was not found microscopically. She was given proluton 5 mg. (hypo) twice daily for the first ten postoperative days. At no time did she show any evidence of threatened abortion.

The patient had an essentially normal antenatal course. She fell into labor spontaneously during the thirty-fifth week of the gestation and was delivered of a 2,390 Gm. male child in good condition, by indicated low forceps after a total labor of 2 41/60 hours. The blood pressure was normal and the urine showed no albumin. There was moderate ante-partum and intrapartum bleeding, and the placenta showed a small area of premature separation.



Figs. 7 and 8.—Low and high power studies of the left ovarian cyst wall, demonstrating the epithelium lining the cyst and the underlying decidual reaction and ovarian stroma.

### Summary

This is a 23-year-old white female who had a grapefruit-sized endometrial cyst of the right ovary removed and a small endometrial cyst resected from the left ovary when 10 to 12 weeks pregnant. At operation there was a small amount of free, chocolate material scattered over the pelvis, and the patient had experienced some lower abdominal discomfort for about one month before operation. Both endometrial cysts showed areas of decidual reaction. She subsequently delivered precipitously a 2,390 Gm. male child in good condition during the thirty-five week of the pregnancy, and the placenta showed a small area of premature separation.

This patient had experienced no symptoms of endometriosis prior to the pregnancy. She had been married two years and no contraception had been practiced. Her only symptom was discomfort of an aching type in the lower abdomen, and the endometrial cyst had been "leaking," but frank rupture had not taken place.

There are other isolated reports of endometriosis associated with pregnancy found in less common sites.

Rushmore<sup>67</sup> in 1931 described a patient, 26 years old, who had been delivered four years previously by version and extraction and who reported, early in pregnancy, a brownish vaginal discharge. A small, polypoid mass,  $\frac{1}{4}$  inch in diameter, was found just to the right of the cervical os, and biopsy showed endometrial glands and decidual reaction, superficially covered with squamous epithelium. The mass increased two to three times its original size over the subsequent eighteen days, bleeding from the nodule increased, and the pregnancy was interrupted. The pregnancy incidentally was in one horn of a bicornate uterus. Rushmore attributed the cervical endometriosis to the previous version and extraction. Zacherl's<sup>68</sup> case of decidual reaction in a cervical polypoid mass of a 25-year-old patient, eight weeks pregnant, probably represented another case of cervical endometriosis.

Olson and Hansmann<sup>30</sup> did a low cervical cesarean section on a 41-year-old primigravida with a contracted pelvis and fourteen hours of labor. Shotty tubercles were found in the anterior cul-de-sac which revealed microscopically endometrial glands with a wide cuff of decidual cells.

Milnor and Tilden<sup>69</sup> removed an inguinal, thin-walled cyst from a 38-year-old toxemic patient upon whom they did a therapeutic abortion. The inguinal tumor had enlarged and caused increasing discomfort with pregnancy. This patient had had one living child and two previous therapeutic abortions. The cyst wall revealed endometrial stroma and nodules of decidual cells and also decidual cells were found ectopically on the appendix.

Jenkinson and Brown<sup>18</sup> made a special study of endometriosis of the rectum and sigmoid colon. Intestinal endometriosis is infrequent; intestinal endometriosis of the small intestines is very rare. Haufli's<sup>70</sup> case represents one of the most dramatic of all the cases reviewed. A diagnosis of acute appendicitis was made in a 30-year-old patient who was 6 months pregnant. A generalized peritonitis was found, originating from a perforation of the small intestine, and 17 cm. of small intestine was resected. A 2-cm. "knot" in the intestinal wall at the site of the perforation showed decidual reaction in an area of endometriosis.

Endometriosis in postoperative scars was found in 31 instances at Mayo Clinic by Wyrens and Randall,<sup>71</sup> according to their report in 1941. Martin, Michon, and Pigeaud<sup>72</sup> in 1933 stated that an endometriosis of a section scar grew with a new pregnancy. His patient was 37 years old. Harbitz<sup>29</sup> has collected a tremendous number of original and literature cases of abdominal scar endometriosis. He described a patient, 34 years old, who four years after a cesarean section had endometriosis of the abdominal scar excised. The painful lump again recurred, but three years later, during a pregnancy, the pain in the scar endometriosis entirely disappeared. The area was subsequently excised for the second time.

The average age for twenty-five of the preceding cases, in which the age was given, and including two new cases reported in this article, was 31.5 years. In eight of the cases the parity was not given, six were pregnant for the first time; seven had had one previous, one had three previous, one eleven previous pregnancies, and two were listed only as multiparas.

### Conclusions

Despite the relative and absolute sterility statistics so frequently given for patients with endometriosis, the collected series of internal and external endometriosis cases complicating pregnancy is evidence enough that such patients can and do become pregnant. This fact alone should deter physicians from painting too black a picture to these patients as regards future childbearing. It should enhance the plea, so often given, that whenever possible, and particularly when the patient desires preservation of the childbearing function, to be conservative in the surgical procedure. This necessarily demands an intimate knowledge of the patient, a comprehension of her emotional and intellectual make-up, as well as a sufficiently accurate preoperative diagnosis in order that possibilities may be considered and discussed with the patient. Such a surgeon-patient relationship is fundamental, yet as surgical mass production clinics increase and socialized medicine becomes nearer to being a reality, this contact is the hardest kind to maintain. Let this one small voice enter a note of hope that somewhere, somehow, a suitable compromise may be found.

Undoubtedly, many cases of unrecognized endometriosis become pregnant and deliver without complications serious enough to warrant a procedure that would definitely establish the coexistence of the two processes, one pathologic and the other physiologic. On the other hand, gynecologists and obstetricians should be familiar with the ways in which endometriosis may manifest itself during pregnancy, and therefore, should include this disorder in their list of "possible causes."

Internal endometriosis (adenomyoma or adenomyosis) may cause an asymmetry of the uterus, indistinguishable from myomatous changes, or from a cornual pregnancy. It is, possibly, a reason for spontaneous rupture early or late in pregnancy, or may be the factor, on rare occasions, for uterine perforation at the time of therapeutic or criminal abortion. Internal endometriosis was the explanation for uterine atony

and post-partum hemorrhage in three cases in the literature. The tumor mass may be a dystocia factor, necessitating operative delivery. There is some evidence, admittedly scant, that this type of endometriosis is an element in the production of spontaneous abortions and miscarriages, ectopic pregnancies, and placenta previa. Endometriosis is sometimes partially to blame for these accidents, merely because it represents a uterine abnormality and not because of any special peculiarity of the pathologic process.

External endometriosis complicating pregnancy is most commonly found, according to the literature, in the cul-de-sac of Douglas. Usually this is symptomatic because of a vaginal extension, and the patient complains of a brownish or frankly bloody vaginal discharge during the pregnancy. Such a complaint was also given in those cases with cervical endometriosis. It is obvious that such a patient could be erroneously diagnosed as having a threatened or inevitable abortion, and unless speculum vaginal examinations and a sterile pelvic examination are done, the treatment may be disastrous to the patient and to the pregnancy. A biopsy should be obtained, in which case the pathologic process is proved. The biopsy is proof only if properly interpreted by a competent gynecologic pathologist, for in one of the previously reported cases the lesion was interpreted as a "squamous epithelioma of the vagina." A palpable mass may be found in the cul-de-sac which might give some concern as a dystocia factor during labor. According to the cases reviewed these masses are seldom of such a size as to cause any obstruction to delivery; they are often spongy and pliable, and although they frequently increase in size for the first four months, they generally become smaller in the last half of pregnancy.

Ovarian endometriosis, the second most commonly reported type found during pregnancy, is clinically recognized in several ways. An ovarian cyst may be palpated during pregnancy, and unless there are very definite complaints in the history suggesting endometriosis (a situation strikingly rare in the cases in the literature and in the two cases reported in this article), the fact that the cyst is endometrial will probably escape notice. If a laparotomy is decided upon, depending upon the individual case indications, the diagnosis can be made from the associated "tell-tale" pelvic findings and from the pathologic studies. If these symptoms are observed throughout pregnancy, it is unlikely that in the absence of cyclic endometrial changes the cyst will enlarge. The cyst may produce symptoms because of slow and occasional leaking, produced, not by intermittent hemorrhage into the cyst with increasing tension, but by increased countertension by the enlarging uterus upon an already tense cyst. Such was the situation found in Case 2 in this report. Another more sudden and dramatic episode of acute abdominal pain can result from an actual rupture of the cyst and extensive peritoneal irritation. Endometrial cysts are usually adherent and con-

sequently less amenable to intra-abdominal adjustment. They may be attached to the uterus, as was the cyst which ruptured in Case 1. In this case, as the uterus enlarged, the adherent bands of the endometrial cysts were unable to stand the increased pull and separation, and either a slow leak or a sudden escape of all of the cyst content was the result. The fact that the cysts are usually adherent explains the infrequency with which they twist. Certainly, many endometrial cysts are coincidental and the pregnancy proceeds uncomplicatedly to a normal delivery and puerperium without the patient or the physician being aware of the cyst's existence. For the peace of mind of the obstetrician and the patient and for the welfare of the pregnancy, this situation is often a fortunate one.

When encountered during pregnancy, endometriosis of the external type outside the cul-de-sac of Douglas and the ovarian regions is usually an incidental finding, and symptoms are rare. An abdominal scar endometriosis is usually asymptomatic during pregnancy, except possibly for slight enlargement. An inguinal endometrial cyst was reported to have enlarged during pregnancy. Mention should be made of the coincidental findings of tubal and ovarian pregnancy associated with tubal and ovarian endometriosis. Peritonitis following intestinal rupture through an area of endometriosis in the small intestine during pregnancy is certainly a rare, almost "freak," case.

Finally, let every gynecologist and obstetrician realize that patients with endometriosis *can* and *do* become pregnant, that this endometriosis *can* and *does* cause symptoms during pregnancy, and that in the surgical treatment of endometriosis preservation of the childbearing function *should* always receive consideration.

### Discussion

1. Endometriosis, or at least the diagnosis of endometriosis, is on the increase. The greatest incidence of endometriosis is found in the latter half of the fourth decade of life, and its selectivity for the higher social-economic strata of society is shown by Meigs' statistics of 36 per cent gross diagnosis in private abdominal cases as compared to 8.3 per cent gross diagnosis in the ward abdominal cases at Massachusetts General Hospital.

2. A discussion of endometriosis and pregnancy is in some measure a paradox. Eighty-eight per cent is the normal fertility rate in marriage, according to Reynolds and Macomber. Counseller found 48.9 per cent relative and 32.1 per cent absolute sterility in 131 married endometriosis cases. Other authors have found a similar high sterility rate in their groups of endometriosis cases. Associated pathologic processes, such as myomas, endometrial hyperplasia, etc., are common. The dyspareunia, metrorrhagia, and menorrhagia found in endometriosis may serve to reduce the frequency of coitus.

3. Ectopic decidual formation is discussed, and the similarity in its distribution to the distribution of endometriosis is pointed out—both diminish in incidence as the distance from the ovaries increases.

4. Endometriosis is divided into internal and external types, according to the location of ectopic endometrial tissue inside or outside the uterine body musculature.

5. Several cases of internal endometriosis (adenomyoma or adenomyosis) and pregnancy are found in the literature. In most of the reports a diagnosis of a myomatous uterus was the indication for laparotomy. Five cases of uterine rupture during pregnancy were reported in the literature; endometriosis showed microscopically in sections through the areas of rupture. Uterine atony and post-partum hemorrhage in three cases were explained on the basis of internal endometriosis. The adenomyoma in two cases was a dystocia factor, indicating delivery by cesarean section. One ectopic pregnancy was found by Sampson in an area of cornual adenomyoma, after an attempted tubal sterilization. Internal endometriosis may or may not be a factor in the production of spontaneous abortions, miscarriages, and placenta previa. In the twelve cases of internal endometriosis and pregnancy where the ages were given, the average age was 36.1 years. Of ten of these cases, four were primigravidas.

6. External endometriosis complicating pregnancy is most common in the rectovaginal septum and ovarian regions.

7. Rectovaginal endometriosis, usually arising from the cul-de-sac of Douglas, may present symptoms mimicking threatened or inevitable abortion, and the accurate diagnosis and treatment depend upon speculum and pelvic examination, together with biopsy confirmation whenever possible. Eleven cases of this type of endometriosis and pregnancy were found in the literature. One case, 27 years old, married less than two years, had three children, all under one year of age after a series of complications. Rectovaginal endometriosis was frequently found to increase in size up to the fourth month of pregnancy and then regress in size until term.

8. Ovarian endometriosis and pregnancy were reported seven times in the literature. One case was ovarian endometriosis and an ovarian pregnancy in the same ovary. Rupture of an endometrial cyst is infrequent, and no case was found in the literature of this complication during pregnancy. Case 1, encountered in our clinic, was a 25-year-old primigravida who had an exploratory laparotomy and cesarean section, hysterectomy, bilateral salpingo-oophorectomy because of the rupture of one of two endometrial cysts in the thirty-sixth week of pregnancy. The rupture was the result of the tearing of the adherent cyst wall by the enlarging uterus. Case 2 was a 23-year-old female who had a large endometrial cyst of the right ovary and a small endometrial cyst of the left ovary encountered at a laparotomy when she was twelve



weeks pregnant with her first pregnancy. A right salpingo-oophorectomy, resection of the left ovarian cyst, and appendectomy were done, and she delivered in the thirty-fifth week of the pregnancy a 2,390 Gm. male child.

9. Two cases of cervical endometriosis, one of anterior cul-de-sac endometriosis, one of an inguinal endometrial cyst, one of small intestinal endometriosis with perforation and peritonitis, and two of abdominal scar endometriosis were found associated with pregnancy in the literature.

10. The average age, of twenty-five cases of external endometriosis and pregnancy, was 31.5 years. Of seventeen cases where the parity was given, six were pregnant for the first time.

11. A decidual reaction of the endometrial stroma in these cases of endometriosis and pregnancy was an almost constant finding, as would be expected.

12. Many cases of unrecognized endometriosis go through pregnancy and the puerperium without complication. The ways in which it may complicate pregnancy are discussed.

13. A plea is entered for conservative pelvic surgery whenever possible in cases of endometriosis, for they *can* and *do* become pregnant.

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## CAUDAL ANALGESIA: AN EXPERIMENTAL AND ANATOMICAL STUDY\*

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EDWARDS and Hingson,<sup>1</sup> to whom credit is properly given for introducing continuous caudal analgesia into the field of obstetrics, have proposed that "The fundamental knowledge of the anatomy of the sacral area . . . is a prerequisite for success in continuous caudal analgesia."<sup>2</sup>

Experimental and anatomical studies pertaining to the level of termination of the dural sac, to the size of the sacral hiatus, and to the disposition of solutions injected into the epidural space of the vertebral canal through the sacral hiatus have been reported. Farr,<sup>3</sup> Shaw<sup>4</sup> and Elliott<sup>5</sup> injected fresh bodies a short time after death and noted the heights reached by varying amounts of solution. In addition to similar experiments Brenner<sup>6</sup> noted the level of the termination of the dural sac as did Grodinsky and Best.<sup>7</sup> Thompson<sup>8</sup> tabulated his observations on a series of dissecting-room cadavers and noted as well the level of the apex of the hiatus. A search of the literature reveals that study of the anatomy of the sacral area relative to analgesic technique has not been pursued to any extent in the last decade except for the skeletal investigations of the sacrum made by Trotter and Letterman.<sup>9, 10</sup> A question of significance in the problem of the technique of continuous caudal analgesia not yet answered is that of the distance between the level of termination of the dural sac and the apex of the hiatus.

This report is concerned with (1) the level in the epidural space to which a given amount of fluid injected through the sacral hiatus will pass, (2) a comparison of the size of the hiatus sacralis in the recent and skeletonized state, and especially (3) the distance between the caudal end of the dural sac and the apex of the hiatus sacralis.

### Material and Methods

A series of 56 cadavers, 46 males and 10 females, comprised the material. The majority of these were prepared especially for this study; they were embalmed and then immersed in a tank of 3 per cent carbolic acid until two days before use. The exceptions are: nine which were used for routine class dissection and had been disarticulated between the third and fourth thoracic vertebrae; and one which had been dissected also and had been disarticulated between the fifth lumbar and first sacral when it reached us.

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The entire procedure was as follows :

1. A special malleable,  $2\frac{1}{2}$  inch, 19 gauge needle with stylet<sup>11</sup> was inserted into the midline of the sacral hiatus as determined by palpation.

2. The skin, subcutaneous tissue, and muscles were reflected exposing the spinous processes and laminae of the presacral vertebrae. The ligamenta flava and other articular ligaments were undisturbed. The soft parts over the dorsum of the sacrum were left intact.

3. Thirty or sixty c.c. of a combined aqueous solution of a radio-opaque substance and a dye were injected (by the same person and as rapidly as the tissues permitted) ; lead acetate or lead nitrate was used for the former, a 5 per cent acid fuchsin for the latter.

4. In 12 of the cases the solution was introduced and followed under the fluoroscope.

5. In two-thirds of the cases the injection was made with the body prone; this position was maintained throughout the entire procedure. In the remaining one-third the injection was made with the body resting on the right side in a true lateral position after which it was immediately turned supine.

6. Fifteen minutes after the colored opaque solution had been introduced, the vertebral canal was exposed. Removal of the laminae and spinous processes was accomplished by parallel saw cuts made just medial to the articular processes. Observation of the disposition of the dye was made at this time.

7. The dorsum of the sacrum and especially its hiatus was now laid bare of the soft parts. Measurements were made of the hiatus: width of base, length, and anteroposterior diameter of the sacral canal at the apex of its hiatus. The level of the apex of the hiatus was marked on the ventral wall of the canal by insertion of an ordinary dress-maker's pin.

8. The dorsal wall of the sacral canal was removed usually in one piece after appropriate saw cuts. By this procedure the dural sac was exposed, examined, and its lower limit demarcated by insertion of another pin. The distance between the two pins on the anterior wall of the sacral canal was measured with a flexible steel tape.

9. The sacrum was skeletonized (after the method described by Terry<sup>12</sup>) and all the above measurements repeated on the cleaned bones.

### Levels Reached by Solution

In forty-nine bodies injections of 30 c.c. of the combined solution were made uniformly into the epidural space through the hiatus of the sacral canal. Since two different positions were used for the bodies (33 prone, 16 lateral-to-supine) the results will be considered in two groups according to position. The dye reached the level of the foramen magnum twice as often when the body was prone as when it was in the true lateral and then turned supine. In five bodies in the prone position the dye did not get beyond the level of the sacrum whereas this result was not obtained in the other group. In both groups the distribution of the injected fluid was scattered at various levels between the sacrum and foramen magnum. In the prone position there appeared to be some concentration in the lumbar and lower thoracic region and in the lateral-to-supine position the dye reached the upper thoracic region in the majority of bodies. The vertebral levels attained infrequently or not at all were the upper thoracic for the prone

group and the cervical vertebrae for the lateral-to-supine group. A graphic representation of the levels reached by the solution in both groups is made in Fig. 1 (A and B) and a summary (in per cent) is given in Table I.

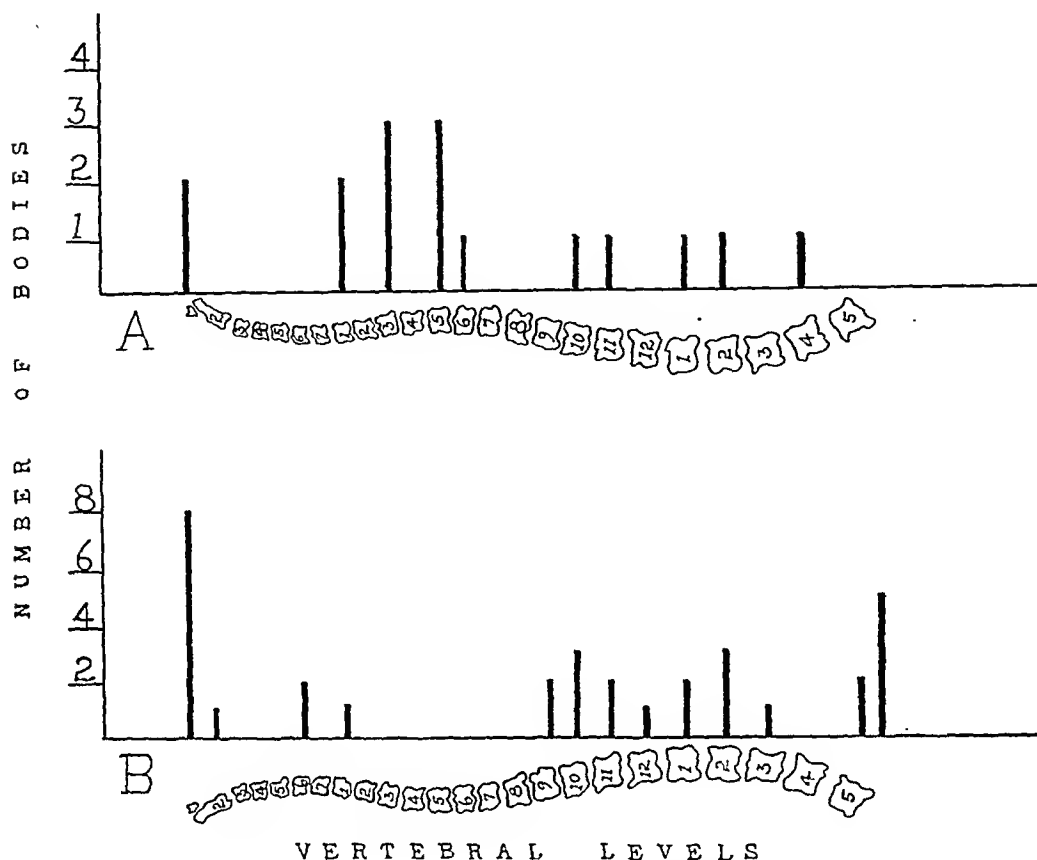


Fig. 1.—Levels reached by 30 c.c. of combined solution injected into the epidural space through the hiatus of the sacral canal. (The outlines of the column were taken from H. Virchow, *Anat. Anz., Ergänz. Heft 38, 1911.*)

A. Cadavers (16) were in a true lateral position and turned supine immediately after the injection.

B. Cadavers (33) were in the prone position.

Assuming that the vertebral bodies are equal units, it was determined that the mean reached by the solution in cadavers in the prone position was the seventh thoracic and in the lateral-to-supine position the fifth thoracic vertebra.

TABLE I. THE REGIONAL LEVELS (IN PER CENT) REACHED BY 30 C.C. OF SOLUTION INJECTED INTO THE EPIDURAL SPACE THROUGH THE HIATUS OF THE SACRAL CANAL ACCORDING TO POSITION OF THE CADAVER

LEVELS	PRONE	LATERAL-TO-SUPINE	BOTH	TOTAL NUMBER OF BODIES
Sacrum	15.2	0	10.2	5
Lumbar	24.2	18.8	22.5	11
Lower 6 thoracic	24.2	12.5	20.4	10
Upper 6 thoracic	3.0	56.2	20.4	10
Cervical	9.2	0	6.1	3
Foramen magnum	24.2	12.5	20.4	10
Total	100.0	100.0	100.0	49

The dye was deposited in the subarachnoid space in two cases. In one the distance between the apex of the hiatus and the lower limit of the dural sac was 58 mm., in the other 40 mm.; both distances are well within the overall length of the shaft of the malleable needle. In these bodies the dye was found in the epidural space as well and had reached the level of the foramen magnum.

In twelve bodies in the lateral-to-supine position the injection was made under the fluoroscope. The fluid traveled rapidly and reached its ultimate level in the epidural space immediately.

In three cadavers, all in the prone position, 60 c.c. of solution were injected: in one, the dye reached the level of the foramen magnum, in another it passed only to the level of the fifth lumbar vertebra and in the third the solution had had some gelatin added and was not found above the level of the tenth thoracic vertebra. In three more cadavers, again in the prone position, the solution extended all the way to the point where disarticulation had been made between the third and fourth thoracic vertebrae. One cadaver (the fifty-sixth) was not injected since it had been disarticulated between the fifth lumbar and first sacral vertebrae.

### Size of Hiatus in the Recent and Skeletonized States

In the series of 56 bodies only 53 sacra could be used for measurement of the hiatus sacralis in the recent state. Two had complete agenesis of the dorsal wall; part of the bone had been eroded away by a decubitus in the remaining one, and finding the outline of the hiatus was impossible. During skeletonization the dorsal wall of the sacral canal of three specimens disintegrated to such an extent that measurements of the hiatus could not be repeated. Therefore, data are present for only 50 cleaned sacra.

A comparison of measurements made on the hiatus of the sacral canal in the recent state and of those made on the skeletonized sacra is summarized in Table II. There was no statistically significant difference between the means of any of the three pairs of measurements.

TABLE II. MEANS IN MM. (IN THE RECENT STATE AND AFTER SKELETONIZATION) OF WIDTH OF BASE OF HIATUS, OF LENGTH OF HIATUS AND OF ANTEROPOSTERIOR DIAMETER OF THE VERTEBRAL CANAL AT THE LEVEL OF THE APEX OF THE HIATUS

	IN THE RECENT STATE	AFTER SKELETONIZATION
Width of base	18.0 $\pm$ 0.3	19.3 $\pm$ 0.3
Length of hiatus	26.3 $\pm$ 1.0	25.3 $\pm$ 0.9
Anteroposterior diameter	5.8 $\pm$ 0.2	6.1 $\pm$ 0.2

The anteroposterior diameter of the vertebral canal at the level of the apex of the hiatus was three mm. or more in all cases. There was no difficulty in the procedure of insertion of the needle.

The mean level of the apex of the hiatus was found to be the lower third of the fourth sacral vertebral body. In 38.4 per cent of the cases the apex was at a level cephalad to the mean with the highest occurring at the joint between the second and third sacral vertebrae. (Fig. 2, broken lines.)

### Distance Between Dural Sac and Apex of Hiatus Sacralis

The point of termination of the dural sac occurred between the levels of the middle of the first and the middle of the third sacral vertebral bodies. The mean point was the middle third of the body of the second sacral vertebra. Of the 56 sacra studied, the termination of the dura was at a level cephalad to the mean in 37.5 per cent and caudad in 46.4 per cent. In no case was there observed a partition, fenestrated or otherwise, extending between the dorsal surface of the dura and the dorsal wall of the vertebral canal. However, the dura in one of the two bodies in which the solution entered the subarachnoid space was quite tightly adherent to the dorsal bony wall of the canal in the sacrum.

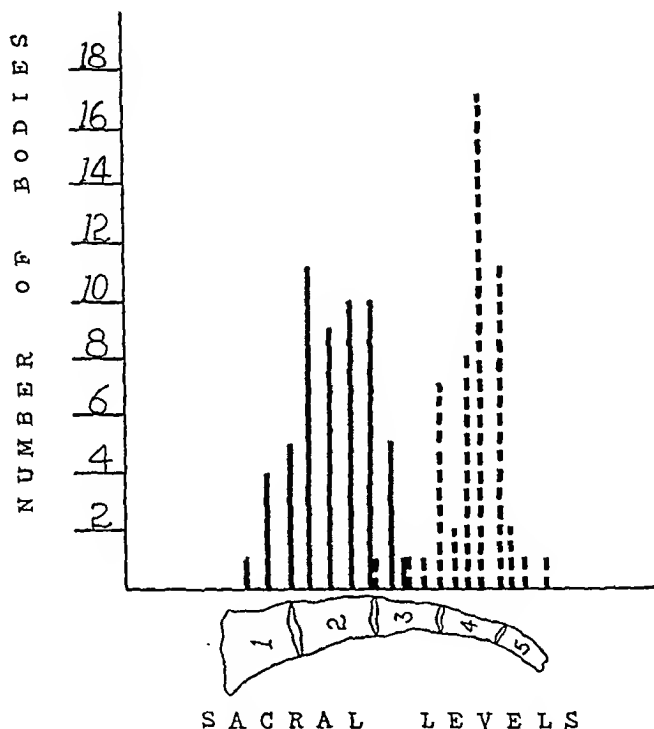


Fig. 2.—Levels of the inferior extent of the dural sac (solid lines) and of the apex of the hiatus of the sacral canal (broken lines).

The same 53 cases used in determining the size of the hiatus (in the recent state) afforded measurements of the distance between the apex of the hiatus and the termination of the dural sac before and after skeletonization. There was no significant difference between measurements made under these two conditions. The mean distance was 47.4 mm. on the cleaned bones with a range of 19 to 75 mm. A summary of the measurements is given in Table III.

Thus, it may be seen that there was 42 per cent of the cases with a shorter distance between the apex of the hiatus and the dural sac than the mean distance.

A diagrammatic representation of the inferior limit of the dural sac and of the superior limit of the apex of the hiatus is made in Fig. 2. A correlation between the level of the apex (the superior limit at which the needle might be passed into the sacral canal) and the distance from the apex to the dural sac was not obtained.



TABLE III. INCIDENCE OF THE DISTANCES BETWEEN THE APEX OF THE HIATUS AND THE LOWER EXTENT OF THE DURAL SAC; PERCENTAGE INCIDENCE OF THE MEAN AND OF THOSE DISTANCES SHORTER AND LONGER THAN THE MEAN

DISTANCE IN MM.	NUMBER OF BODIES	PER CENT
16 to 20	1	
21 to 25	1	
26 to 30	5	
31 to 35	5	42.0
36 to 40	3	
41 to 45	7	
46 to 50	12	22.0
51 to 55	5	
56 to 60	5	
61 to 65	2	36.0
66 to 70	3	
71 to 75	4	
Total	53	100.0

### Discussion

The levels reached by a given amount of solution injected into the epidural space through the sacral hiatus of embalmed cadavers were found to vary throughout the extent of the column. Similar findings were obtained by Thompson<sup>8</sup> and by Grodinsky and Best<sup>7</sup> who have experimented on the embalmed cadaver. The reports on fresh bodies by Shaw,<sup>4</sup> Farr<sup>3</sup> and Elliott<sup>5</sup> indicate that the levels reached were proportionate to the amount of solution injected. Brenner's report<sup>6</sup> is the exception, if his material is correctly assumed to be embalmed cadavers; he found the level to be determined by the amount of solution injected. The results may be summarized as follows:

AUTHOR	DATE	NUMBER OF BODIES	STATE OF MATERIAL	POSITION	TIME OF INJECTION	AMOUNT INJECTED	LEVEL REACHED PROPORTIONATE TO AMOUNT?
Thompson	1917	30	Embalmed	?	?	30 c.c.	No
Brenner	1924	?	Embalmed?	?	?	20 to 120 c.c.	Yes
Shaw	1926	11	Fresh	?	5 min. after death	15 to 17 c.c.	Yes
Farr	1926	2	Fresh	"Lateral-horizontal"	12 hrs. after death	30 to 118 c.c.	Yes
Elliott	1926	8	Fresh	?	3 to 6 hrs. after death	30 to 120 c.c.	Yes
		1	Living	?		?	Yes
Grodinsky and Best	1929	12	Embalmed	Prone; 3 with head raised	?	30 to 100 c.c.	No
Present study	1944	52	Embalmed	36 prone 16 lateral-to-supine	More than 30 days after death	30 c.c.	No
		3	Embalmed	Prone	More than 30 days after death	60 c.c.	No

It would be of value to have reports on a larger series of fresh bodies and on the living for comparison with levels reached in the embalmed cadaver.

Farr<sup>3</sup> states that “. . . the position in which the patient is placed during, or directly after, the injection may have some bearing on the results.” It is suggested by these cadaver experiments that the position of the body at the time of injection may contribute to the determination of the level reached. In the prone position there was some tendency for the solution to travel no farther than the lumbar or lower thoracic region whereas in the lateral-to-supine position the dye tended to reach the upper thoracic region. However, the solution reached the level of the foramen magnum twice as frequently when the body was prone as when it was lateral and then turned supine. It is unfortunate that of all the investigators only Grodinsky and Best<sup>7</sup> have considered different positions of the body. They placed all the cadavers prone and for three the head was raised; no differences resulting from the varied positions were pointed out. Observations of the solution under the fluoroscope showed that it traveled quickly and reached its superior level immediately. Thus, it would be accurate to consider the “lateral-to-supine” position as “lateral,” for after the body was turned supine there was no apparent alteration in the height reached by the solution.

It was of interest that in the two bodies whose dura was punctured, the solution in the epidural space reached the level of the foramen magnum. The obvious explanation of the solution being deposited in both the subarachnoid and epidural spaces is supplied by the needle which has an opening not only at the tip but also in the wall close to the tip. Presumably the tip of the needle had just pierced the dura, whereas the opening in the wall of the needle allowed fluid to escape into the epidural space. This is evidence that an amount of solution smaller than 30 c.c. can easily travel to the level of the foramen magnum in the embalmed cadaver.

The mean measurements of the hiatus of the sacral canal were not significantly different before and after skeletonization. As might be expected the measurements taken on the sacra in the recent state are somewhat smaller than those taken after skeletonization excepting the one of the length of the hiatus. This may be explained by the fact that it is not always possible to determine on sacra in the recent state the exact level of the base of the hiatus. The strong, dense superficial posterior sacrospinous ligaments may simulate elongated sacral cornua and thus the level of the base of the hiatus can be interpreted to be too far caudad with the resultant increase in length; this was the condition in several cases of this series. The means of the skeletonized sacra are slightly greater than those reported by Trotter and Letterman<sup>9, 10</sup> but the differences are expectedly insignificant since the source of the material and the method of preparation were the same for both

studies. The mean level of the apex is at the lower third of the fourth sacral body but in 38.4 per cent of the series it lies at a level cephalad to this plane. If the needle should be inserted at the apex there is increased danger of puncturing the dural sac. Earlier reports<sup>9, 10</sup> have presented even higher percentages.

The inferior extent of the dural sac is generally described as occurring at the level of the second sacral vertebra.<sup>13-16</sup> In this series of cadavers the mean level was at the middle third of the second sacral vertebra. Brenner<sup>6</sup> examined the termination of the dural sac but did not tabulate his results or state the number of sacra examined. Thompson<sup>8</sup> listed the level of termination in 14 cases; of these, three were between the bodies of the second and third sacral vertebrae and four at the level of the body of the third sacral vertebra. In the 12 cadavers examined by Grodinsky and Best<sup>7</sup> the dural sac ended at the level of either the first or second sacral vertebra. In the 56 cases of the present study the termination of the dural sac was caudad to the level of the body of the second sacral vertebra in 28.6 per cent or 16 cases. However, the level of the termination of the dural sac is significant in the administration of continuous caudal analgesia chiefly in its proximity to the level of the apex of the hiatus of the sacral canal. Since the apex of the hiatus was found to be cephalad to the mean (lower third of fourth sacral body) in more than one-third of the cadavers and the dural sac extended caudad to the mean (middle third of second sacral body) in almost one-half of the series, the distance between the two was very much reduced over that classically described.

The mean distance between the apex of the hiatus sacralis and the termination of the dural sac was 47.4 mm. Two different lengths of needles are recommended for use clinically, a 3 inch (76 mm.) and a 2½ inch (63 mm.) needle. If allowance of 10 mm., which may be considered average, is made for skin and subcutaneous tissue there is left a 66 mm. or 53 mm. length of needle to lie in the canal. The distance between the apex and the dural sac was less than 66 mm. in 86.8 per cent or 46 of the 53 cases and less than 53 mm. in at least 64.2 per cent or 34 cases. From this the importance is seen of the step in the procedure which instructs one to depress the hub of the needle after its tip enters the canal but before the full length of its shaft is driven in. Thus, the point is elevated so that it may approximate the dorsal wall of the sacral canal and thereby avoid the dura which is adherent to the ventral but usually free from the dorsal wall.

### Summary

1. Experimental and anatomical studies pertaining to continuous caudal analgesia were carried out on 56 embalmed cadavers.

2. Levels reached by a constant amount of combined solution injected into the epidural space through the hiatus of the sacral canal varied throughout the extent of the column. These results compared

favorably with the results of others who have utilized embalmed cadavers but did not agree with the findings obtained by workers who injected fresh cadavers.

3. Measurements of the dimensions of the hiatus canalis sacralis were not significantly different before and after skeletonization.

4. The mean level of the apex of the hiatus was found to be the lower third of the body of the fourth sacral vertebra. In 38.4 per cent the level was cephalad to the mean.

5. The mean level of the termination of the dural sac was the middle third of the body of the second sacral vertebra; in 46.4 per cent of the bodies examined it extended caudad to this level.

6. The mean distance between the apex of the hiatus canalis sacralis and the inferior extent of the dural sac was 47.4 mm.; in 42 per cent of the cases the distance was less than the mean. In 86.8 per cent the lower limit of the dura could have been reached by the 3 inch needle; in 64.2 per cent by the 2½ inch needle (after allowing 10 mm. for skin and subcutaneous tissue).

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## THE TREATMENT OF PROTHROMBINOPENIA WITH A WATER-SOLUBLE MENADIONE

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POTENTIAL danger of hemorrhage in the newborn infant has long been recognized but determination of its cause has until recently baffled investigations.

Quick and Grossman<sup>1</sup> reported that, with recognition of prothrombin deficiency as a cause of hemorrhage and discovery that vitamin K is essential for synthesis of prothrombin, came a new approach to study and control of hemorrhagic disease of the newborn infant.

Quantitative determination of blood prothrombin in newborn infants by Quick's method shows that, at birth, blood prothrombin is relatively high, about 60 to 75 per cent of the normal adult value. Soon after birth, however, blood prothrombin decreases sometimes to a very low level. Prothrombin is lowest on the first day, higher during the second and returns to normal after the third day. Many of our cases, as shown by the charts, did not return to normal until after the fifth or seventh day. All the cases, however, with appropriate treatment returned to normal by time of discharge on the tenth day.

Prothrombinopenia may occur with or without jaundice and with or without bleeding. There is no definite relationship between the degree or duration of icterus and prothrombin deficiency. However, prothrombin levels approaching dangerous conditions are encountered most frequently in jaundiced patients.

When the prothrombin time was above 18 seconds in our series (Quick method) the infants invariably became jaundiced on the third day. In former years the explanation of this onset of icterus was that it was purely hemolytic, a result of the reduction of the polycythemia of the fetus with the production of bilirubin more rapidly than the liver is able to excrete it. However, Salmon and Richman<sup>2</sup> state that, if this is the only factor, there should be some demonstrable relationship between the degree of blood destruction and the degree of hyperbilirubinemia. Not all investigators have found this to be true.

Investigations of changes in the erythrocyte fragility seen during the neonatal period have shown results to be at variance.

Physiologic icterus of the newborn infant, in so far as is known, in no way impairs the health or well-being of the infant and is seen so frequently as to be looked upon as a normal occurrence. However, this

finding has been the subject of considerable investigation, not so much for its own importance, as for the possibility that it might reflect certain other important physiologic changes of the neonatal period.

Whatever the significance may be, we found that a great many infants developed icterus on the seventh day whose mothers gave a history of having had either gallbladder disease, diarrhea or colitis. This may give us a clue as to what method of treatment should be followed before the mother is delivered and what to expect in the way of newborn phenomena.

Adoption of early diagnostic laboratory methods at the time of delivery will, in many cases, reward the vigilant obstetrician. Indeed, such procedures instituted at our hospital during this study more than doubly rewarded the staff members in seeing many of their cases saved from certain death.

Ross and Malloy,<sup>3</sup> Russell and Page,<sup>4</sup> McCreedy, et al.<sup>5</sup> report excellent results with the use of vitamin K in raising the prothrombin levels and decreasing the incidence of spontaneous hemorrhage in their series.

Fitzgerald and Webster<sup>6</sup> have found that the normal depression of the prothrombin level, which occurs from the second to the fifth day after birth, is much greater when barbiturate analgesics are used during labor. They believe that administration of vitamin K to the mother during labor will prevent this further depression and lower the incidence of hemorrhage of the newborn infant, and that vitamin K should, therefore, be given when barbiturate analgesics are used.

Finally, Clifford et al.<sup>7</sup> recommended that vitamin K be universally used to prevent the hypoprothrombinemia of the newborn and thereby protect the infant during any possible period of trauma, asphyxia, sepsis or other hazards. They favor administration of vitamin K to the mother, although they state that "to provide every possible protection in the light of our present knowledge and experience, every newborn baby could well be given vitamin K at birth whether or not there has been previous maternal administration."

One of our aims in making this study was to determine the value of a synthetic vitamin K, without the administration of bile, for obviously we could not give the newborn infant any medicinal bile. It had to be of necessity a water-soluble (injectable) vitamin K, or "menadione," in ampoule form to be given by intramuscular injection. Then a tablet without medicinal bile to the mother.

The results of our investigations are herein presented. The period of observation ran for six months, August, 1943, through January, 1944.

### Clinical Material

Maternity patients admitted to the Menorah Pavilion of the Beth-El Hospital, and their infants in the nurseries. The patients were both private and service. They were predominately primiparas. The birth weight and weight curve did not differ from the average. The majority were artificially fed.

A suitable water-soluble menadione preparation was sought and several were chosen with which to start this series. It was found, however, upon investigation, that these water-soluble preparations were of different strengths. Harrow<sup>8</sup> states that all of these synthetic vitamin K active preparations have greater potency than natural vitamin K and, of these, menadione is the most potent. On a basis of standard units per milligram, menadione rates 1,000 standard units while natural vitamin K rates 300 standard units. Ranking in potency between these two substances, there were several synthetic vitamin K active preparations but none of them were as potent as menadione. Menadione, itself, is oil-soluble and can only be administered effectively in cases of biliary deficiency and obstructive jaundice with the supplementary administration of bile salts. Further, oil solutions are more slowly absorbed by the tissues than a water-soluble preparation. It was found, however, that several preparations of water-soluble menadione were either being marketed or in a state of clinical experimentation and it was decided to try several of these in the following tests.

Because most of these substances produced irritation and pain after injection, only one of these was retained. This was an aqueous solution of menadione and sodium salicylate to which meteyaine (Lilly) had been added. This product\* contained one milligram of menadione per c.c. (1,000 standard units vitamin K activity) and was also available in tablet form, each tablet containing  $\frac{1}{2}$  milligram of menadione (500 standard units vitamin K activity).

### Methods

The blood specimens were taken, at the time of delivery, from both the mother and the infant. The fortuitous coincidence that a quantitative method for determining prothrombin was developed, almost simultaneously with discovery of vitamin K, gave impetus to study of blood coagulation. These studies have solved the problem of controlling certain types of hemorrhage and have given a rational explanation to the blood clotting mechanism. The simplest concept of coagulation was proposed by Morawitz. According to his theory, which is now widely accepted, prothrombin, thromboplastin and calcium interact to form thrombin and this latter agent reacts with the fibrinogen of the blood, changing it to fibrin.

Thus, only four substances are required for coagulation. Since calcium and fibrinogen are very rarely responsible for any demonstrable change in the coagulation process, only prothrombin and thromboplastin remain as factors potentially instrumental in causing disturbance in blood clotting.

Prothrombin occurs only in plasma and is closely associated with the proteins. Thromboplastin is widely distributed in the body, but is intracellular and becomes available only when the cells are ruptured. The amount of prothrombin available, in the blood, to play a part in coagulation, is diminished in the absence of vitamin K.

Quantitative determination of blood prothrombin is indispensable as a guide to therapy of prothrombopenic hemorrhage. Our laboratory used a slight modification of Quick's method. We used 4.5 c.c. of fresh venous blood with 0.5 c.c. of sodium oxalate. This was centrifuged. Then 0.1 c.c. of the plasma was mixed with 0.1 c.c. of thromboplastin

\*Aquione, supplied by Ernst Bischoff Company, Inc., Ivoryton, Conn.

TABLE I. PATIENTS DID NOT RECEIVE ANY VITAMIN K ON ADMISSION (CONTROLS)

CASE NO.	PATIENT	PROTHROMBIN TIME (SEC.)	TIME LABOR	REMARKS
1.	J. K. Para o, grav. i, age 24	18	38' 55"	Manual rotation and midforeeps delivery of a living female child. Patient developed post-partum psychoses.
2.	H. F. Para o, grav. i, age 21	24	3' 10"	Spontaneous delivery of a living male child.
3.	H. S. Para o, grav. i, age 19	20	23' 20"	Low forceps delivery of a living male child.
4.	C. G. Para o, grav. i, age 24	19	2' 55"	Spontaneous delivery of a living male child. Mother a cardiac.
5.	E. G.	26	10' 10"	Spontaneous delivery of a living female child.
6.	H. B.	21	4' 57"	Spontaneous delivery of a living male child. Baby became slightly jaundiced on the seventh day.
7.	C. T.	25	28' 45"	Low forceps delivery of a living child.
8.	L. R.	25	8' 30"	Low forceps delivery of a living child.
9.	J. A. Para o, grav. i, age 22	18	13' 45"	Low forceps delivery of a living female child.
10.	S. W. Para o, grav. i, age 28	24	10' 30"	Low forceps delivery of a living female child.
11.	K.	26	17' 5"	Spontaneous delivery of a living child.
12.	J. P. Age 29	30	13' 58"	Low forceps delivery of a living immature female Mongoloid. Weight 4 pounds 14 ounces. Height 18 inches.
13.	A. M.	24	7' 10"	Spontaneous delivery of a living female child.
14.	R. F.	28	12' 45"	Spontaneous delivery of a living female child.
15.	S. G.	29	5' 59"	Spontaneous delivery of a living female child.
16.	A. S.	25	8' 16"	Spontaneous delivery of a living male.
17.	J. K.	25	30' 15"	Spontaneous delivery of a living female.
18.	H. L.	35	14'	Spontaneous delivery of a living male.
19.	H. M.	18	22' 48"	Low forceps—living child.
20.	E. R.	24	15' 20"	Spontaneous delivery of a living male.
21.	F. S.	27	8' 9"	Spontaneous delivery of a living male.
22.	G.	36	10' 41"	Spontaneous delivery—male. (Baby expired.) Born Oct. 13, readmitted on Nov. 12, died Nov. 12, 1943. Diagnosis: Bronchopneumonia, dehydration.



and quickly added 0.1 c.c. of calcium chloride and watched for the beginning of the clot. Normal is between 10 to 13 seconds. The control was blood from a normal (nonjaundiced) person.

All solutions must be tested before each test and the thromboplastin must always be in ice or kept at freezing temperature. The time from the addition of calcium to the formation of a clot is recorded with a stop watch.

TABLE II. NEWBORN INFANTS OF MOTHERS WHO DID NOT RECEIVE MENADIONE† (CONTROLS)

BABY	MOTHER'S PRO- THROMBIN TIME (SEC.)	CORD PRO- THROMBIN TIME (SEC.)	1ST DAY PRO. (SEC.)	3RD DAY PRO. (SEC.)	5TH DAY PRO. (SEC.)	7TH DAY PRO. (SEC.)	REMARKS
K.	18	20	28	30	21	17	Slight jaundice.
F.	24	18	18	23	19	19	Icteric tinge.
S.	20	22	41	55*	20*	14	Marked jaundice 3rd day.
G.	19	19	18	34	38*	26	Slight jaundice.
G.	26	27	38*	18	20	18	Skin clear.
B.	21	19	15	20		35	Jaundiced. 7th day.
T.	25		21	26	18		Skin clear.
R.	25	53	53*	38*	30*	24	Moderate jaundice.
A.	18		19	18	25	24	Clear.
W.	24	17	18	21	20	18	Clear.
K.	26		20	20	30	27	Slight icteric tinge.
P.	30	27	20	23	33*	23	Infant died. 9th day.
M.	24		20	22	32	22	Clear.
F.	28		28	67*(2)	38*	18	Moderate jaundice.
G.	29		35	27*	23	20	
S.	25	28	21	24	34*	22	Skin clear.
K.	25	21	27	30*	22	24	Slight icteric tinge.
L.	35	24		25	38	22	Skin clear.
M.	18	19	18	18	18		Skin clear.
R.	24	18	20	30*	27	23	Slight jaundice.
S.	27	23	30	24	35	26	Skin clear.
G.	36	55		62*	58*	38*	Marked jaundice.

(Aquinone injection started on fifth day. Other water-soluble preparation used previously.)

\*Ampoules aquinone (menadione) administered to infant after birth for the safety of the newborn.

†Detailed list of the newborn infants from mothers in Table II who didn't receive vitamin K. Vitamin K by ampoule was given only when the prothrombin was prolonged, ½ c.c. in each arm intramuscularly.

In Table V, including mothers and newborn infants, we attempted to determine what significance previous history of either gall-bladder disease, colitis, diarrhea, or prolonged medication had on the prothrombin time. We also took blood smears on all the newborn infants. This point occurred to us after the loss of Case 6 (Table III). Surprisingly we picked up a case (13), a woman, 31 years of age, who had

TABLE III. CASES GIVEN ONE TABLET MENADIONE TREATMENT BY MOUTH AFTER ONSET OF LABOR—ON HOSPITAL ADMISSION

CASE NO.	PATIENT	MOTHER'S PRO-THROMBIN TIME (SEC.)	CORD PRO-THROMBIN TIME (SEC.)	TIME LABOR	REMARKS
1.	G. V. Para i, grav. ii, age 28	14		25' 25"	Low forceps delivery of a living male child. Prenatal period normal.
2.	T. C. Para i, grav. ii age 29	16		5' 43"	Low forceps delivery of a living female child. Prenatal period normal.
3.	R. F. Para i, grav. ii, age 28	15		4' 10"	Spontaneous delivery of a living female child.
4.	J. V. Para i, grav. ii, age 29	17		3' 15"	Spontaneous delivery of a living female child.
5.	M. H. Para ii, grav. iii, age 25	17		3' 48"	Spontaneous delivery of a living male child.
6.	L. S. Para o, grav. i, age 24	65	87	6' 5"	Manual rotation and midforceps delivery of a living male child. Infant had congenital atelectasis and erythroblastosis at birth. Baby expired within a few hours.
7.	H. O. Para i, grav. ii, age 25	15		20' 40"	Spontaneous delivery of a living male child.
8.	S. G. Para i, grav. ii, age 21	18		10' 15"	Low forceps delivery of a living female child.
9.	M. M. Para i, grav. iii, age 34 Premature due October 9th	46	66	13' 5"	History of one stillborn and one miscarriage. Bleeding on admission. Tabs. II of aquinone given. Spontaneous delivery of a living premature—male. Weight 3 pounds 6 ounces.
10.	A. L. Para i, grav. iii, age 31	17		4' 55"	Spontaneous delivery of a living female child.
11.	A. L. Para o, grav. i, age 20	15		11' 20"	Spontaneous delivery of a living male child.
12.	B. H. Para i, grav. ii, age 26	13		6' 37"	Spontaneous delivery of a living female child.
13.	Y. P. Para i, grav. ii, age 21	16		7' 40"	Spontaneous delivery of a living female child.
14.	R. S.	16		12' 58"	Spontaneous delivery of a living child.
15.	M. H.	17		8' 40"	Low forceps delivery of a living child.
16.	M. F.	17		13' 40"	Low forceps delivery of a living child.

TABLE III—CONT'D

CASE NO.	PATIENT	MOTHER'S PRO-THROMBIN TIME (SEC.)	CORD PRO-THROMBIN TIME (SEC.)	TIME LABOR	REMARKS
17.	D. K.	13			Spontaneous delivery of a living child.
18.	T. B.	15			Low forceps delivery of a living child.
19.	M. S.	16			Spontaneous delivery of a living child.
20.	S. B.	14			Low forceps delivery of a living child.
21.	B. W.	20			Low forceps delivery of a living child.
22.	B. La R.	16			Low forceps delivery of a living child.
23.	M.	14			Low forceps. Male.
24.	F. K.	13			Male.
25.	F. R.	14			Male.
26.	N. F.	24			Born Oct. 6, expired Oct. 9. Diagnosis: Diarrhea of the newborn. Female.
27.	E. S.	15			Male.
28.	E. F.	15			Female.
29.	I. B.	16			Female.
30.	A. P.	18			Baby premature.
31.	A. C.	13			Living male child.
32.	S. S.	14			Living male child.
33.	R. L.	13			Living child.
34.	R. S. II.	16			Living child.
35.	E. E.	15			Living female child.

Note: In Table III all cases with exception of cases 6 and 9 showed a prothrombin time within normal limitations.

Case 6: The high prothrombin time of both mother and infant was a clue to hemorrhagic disease in the newborn. Infant died within a few hours of delivery. Diagnosis of erythroblastosis was made on smear taken at time of delivery, and marked secondary anemia, R.B.C. below 2 million.

Case 9: Premature was given adequate doses of vitamin K and was discharged in good condition when infant weighed approximately six pounds.

a cholecystectomy done. Her infant was born in a pool of yellow stained amniotic fluid; blood smear only 2 nucleated cells; expired 16 hours after delivery; prothrombin time 30 seconds. This was a private case and no treatment was given.

Contrast this record with Case 10, male newborn infant with 58 seconds prothrombin. Smear showed 60 nucleated cells. This infant had immediate synthetic vitamin K therapy and made an uneventful recovery. The same result was obtained in Case 18. Here, too, a high prothrombin time was found. Adequate doses of synthetic vitamin K brought the prothrombin down to within normal limits.

Although the original intention of the authors was to follow through the value of synthetic vitamin K without the use of bile salts on both the mother and the infant, the project developed into determining a technique in the early diagnosis of erythroblastosis as a side issue. Several cases showed unusual high prothrombin time and a few had a concomitant increase in nucleated cells. One such case showed as high

TABLE IV. CASES HAD MENADIONE, BLOOD TAKEN FROM MATERNAL SIDE OF CORD AND BABY'S SIDE

CASE NO.	PATIENT	PROTHROMBIN TIME (SEC.)	REMARKS
1.	F. L.	15	Spontaneous delivery.
	Baby L.	20	Slight jaundice on 7th day.
2.	R. R.	16	
	Baby R.	22	Slight jaundice on 7th day.
3.	L. P.	13	
	Baby P.	18	Skin clear.
4.	M. F.	15	
	Baby F.	19	Skin clear.
5.	S.	15	
	Baby S.	19	Readmitted to children's pavilion. Died 10 days after discharge from hospital. Diagnosis: Diarrhea of newborn. Bronchopneumonia.
6.	G.	14	
	Baby G.	17	Skin clear.
7.	W.	13	
	Baby W.	18	Skin clear.
8.	P.	15	
	Baby P.	19	Slight jaundice.
9.	S.	15	
	Baby S.	17	Skin clear.
10.	G.	14	
	Baby G.	21	Slight icteric tinge.
11.	P.	13	
	Baby P.	16	Skin clear.
12.	M. R.	14	
	Baby R.	19	Slightly icteric.
13.	B. B.	16	
	Baby B.	18	Skin clear.

as 3:1 nucleated cells to white cells. This case (Golub) is herein given in detail. We are convinced that the early diagnosis, the transfusion of Rh negative blood, and giving synthetic vitamin K within three hours after diagnosis, were instrumental in saving the life of the newborn infant.

Recently, we discovered another case at the Brooklyn Women's Hospital, a 1-day-old infant (Belkin). Blood count: R.B.C. 1,500,000; nucleated cells 218 to 100 white cells, which after several transfusions of Rh negative blood and aquinone, then showed 3,500,000 R.B.C. and 2 per cent nucleated cells. The transfusion, plus daily intramuscular injections of vitamin K, turned the tide in this newborn infant.

#### Case History

Baby G. (female), birth weight, 7 pounds 11 ounces.

October 27, 1943.—The baby was admitted to the nursery, markedly jaundiced and showed some cyanosis around the lips. Within two hours after admission a blood smear showed 300 nucleated red cells to 100 white cells.

TABLE V. LATER SERIES OF CASES WITH PARTICULAR REFERENCE TO PREVIOUS HISTORY OF CHRONIC ILLNESS OR MEDICATION

DATE	NAME, AGE AND PARA OF PATIENT	HISTORY OF			VITAMIN K QUANTITY AND WHEN	PRO-THROMBIN TAKEN	BLOOD SMEAR TAKEN	RESULTS		CLINICAL REMARKS
		GALL-BLADDER DISEASE,	ULCERATIVE COLITIS	PROLONGED INTAKE OF MEDICATIONS				MOTHERS' PRO-THROMBIN	CORD PRO-THROMBIN	
11/25/43	M. A. Age 24 Para 0, grav. i	Negative.			6 A.M. 1 tablet	10 A.M.	2 nucleated red cells	Q. M.— 15 sec.	Q. M.— 19 sec.	Spontaneous delivery.
		Took treatment for lues at one time.						Normal— 11 sec.	Normal— 11 sec.	
11/26/43	B. Age 27 Para 0, grav. i	Negative			4:45 P.M. 1 tablet	7:40 P.M.	2 nucleated cells	Q. M.— 14 sec.	Q. M.— 17 sec.	Low forceps.
								Normal— 12 sec.	Normal— 12 sec.	
11/29/43	R. Age 20 Para 0, grav. i	Negative			3:30 A.M. 1 tablet	8:20 A.M.	6 nucleated cells	Q. M.— 13 sec.	Q. M.— 18 sec.	Spontaneous frank breech.
								Normal— 12 sec.	Normal— 12 sec.	
11/30/43	R. Age 31 Para 0	Negative			1:30 A.M. 1 tablet	5:05 P.M.	None taken	Q. M.— 14 sec.	Q. M.— 18 sec.	Spontaneous delivery.
								Normal— 10 sec.	Normal— 10 sec.	
11/30/43	G. Age 29 Para 0, grav. i	Negative			8:15 P.M. 1 tablet	4 A.M. 12/1/43	Normal	Q. M.— 14 sec.	Q. M.— 20 sec.	Low forceps. Baby jaundiced on 7th day.
								Normal— 13 sec.	Normal— 13 sec.	
11/30/43	F. Age 29 Para i, grav. ii	Negative			4:18 P.M. 1 tablet	6 P.M.	Normal	Q. M.— 14 sec.	Q. M.— 18 sec.	Spontaneous delivery. Baby jaundiced on 8th day.
								Normal— 10 sec.	Normal— 10 sec.	

12/ 1/43 7.	F. Age 31 Para o, grav. i	Negative	12:15 A.M. 1 tablet	4:20 A.M.	1 nucleated cell	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 19 sec. Normal— 12 sec. (female)	Spontaneous delivery.
11/29/43 8.	A. Age 26 Para o, grav. i	Spastic colitis	9:15 A.M. 1 tablet	11:40 A.M.	1 nucleated cell	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 19 sec. Normal— 12 sec. (male)	Low forceps.
12/ 2/43 9.	R. Age 36 Para i, grav. ii	Negative	12:28 A.M. 1 tablet	1:40 A.M.	3 nucleated cells	Q. M.— 12 sec. Normal— 10 sec.	Q. M.— 17 sec. Normal— 10 sec. (female)	Spontaneous delivery.
12/ 3/43 10.	F. Age 23 Para o, grav. i	Negative	4:15 A.M. 1 tablet	11:55 A.M.	60 nucleated cells Hemoglobin 150%	Q. M.— 55 sec. Normal— 11 sec. (male)	Q. M.— 55 sec. Normal— 11 sec. (male)	Spontaneous delivery.
12/ 2/43 11.	T. Age 25 Para o, grav. i	Negative	8 A.M. 1 tablet	9:15 A.M.	8 nucleated cells	Q. M.— 15 sec. Normal— 10 sec.	Q. M.— 22 sec. Normal— 10 sec. (female)	Spontaneous. Baby jaundiced on 7th day.
12/19/43 12.	M. Age 18 Para o, grav. i	Negative	2:45 P.M. 1 tablet		Normal	Q. M.— 14 sec. Normal— 11 sec.	Q. M.— 17 sec. Normal— 11 sec. (female)	Spontaneous delivery.
12/ 7/43 13.	F. Age 31 Para ii, grav. iv	Cholecystectomy	10:30 A.M. 1 tablet	12:50 P.M.	2 nucleated cells	Q. M.— 28 sec. Normal— 12 sec.	Q. M.— 30 sec. Normal— 12 sec. (male)	Spontaneous delivery. Full of yellowish am- niotic fluid.
<i>Remark:</i> Newborn (Baby F.) was cyanotic and large amount of yellowish stained mucus was aspirated from baby. There was no pres- sure on fetal head during birth. Baby expired 16 hours after birth.								
12/ 9/43 14.	R. Age 29 Para i, grav. ii	Negative	10:30 A.M. 1 tablet		2 nucleated cells	Q. M.— 13 sec. Normal— 11 sec.	Q. M.— 17 sec. Normal— 11 sec. (male)	Spontaneous delivery.

TABLE V—CONT'D

DATE	NAME, AGE AND PARA OF PATIENT	HISTORY OF GALL-BLADDER DISEASE, ULCERATIVE COLITIS PROLONGED IN TAKE OF MEDICATIONS	VITAMIN K QUANTITY AND WHEN	PRO- THROMBIN TAKEN	BLOOD SMEAR TAKEN	RESULTS		CLINICAL REMARKS
						MOTHERS' PRO- THROMBIN	CORD PRO- THROMBIN	
12/9/43 15.	S. Age 25 Para ii, grav. iii	Negative	10 A.M. 1 tablet		1 nucleated cell	Q. M.— 15 sec. Normal— 11 sec.	Q. M.— 18 sec. Normal— 11 sec. (male)	Spontaneous delivery.
12/10/43 16.	G. Age 32 Para i, grav. ii	Negative	8:30 A.M. 1 tablet		6 nucleated cells	Q. M.— 16 sec. Normal— 12 sec.	Q. M.— 20 sec. Normal— 12 sec. (male)	Spontaneous delivery.
12/14/43 17.	R. F. Age 22 Para i, grav. ii	Negative	8 P.M. 1 tablet		1 nucleated cell	Q. M.— 15 sec. Normal— 13 sec.	Q. M.— 19 sec. Normal— 13 sec. (female)	Spontaneous delivery.
12/23/43 18.	M. Age 20 Para i, grav. ii	Negative	4:30 A.M. 1 tablet		6 nucleated cells	Q. M.— 48 sec. Normal— 13 sec.	Q. M.— 65 sec. Normal— 13 sec. (male)	Spontaneous delivery.
12/24/43 19.	W. Age 30 Para ii, grav. iii	Negative	11:35 P.M. 1 tablet		3 nucleated cells	Q. M.— 19 sec. Normal— 13 sec.	Q. M.— 22 sec. Normal— 13 sec. (female)	Low forceps.
12/28/43 20.	M. Age 22 Para 0, grav. i	Negative	7:05 A.M. 1 tablet		3 nucleated cells	Q. M.— 25 sec. Normal— 11 sec.	Q. M.— 28 sec. Normal— 11 sec. (female)	Spontaneous delivery.

Transfusion was ordered and given within two hours of admission, 60 c.c. of Rh negative blood into the scalp vein. Prothrombin time was 72 seconds Quick method, normal 12 seconds.

*October 28, 1943.*—Cyanosis and airhunger still present. Marked icterus to the skin, selera and fingerbeds. Prothrombin time was 120 seconds Quick method, normal 13 seconds.

*October 29, 1943.*—Complete blood count and smear taken—showed as follows:

15.4 Gm. = 100% hemoglobin	Macrocytosis	3+
R.B.C. 2,500,000	Microcytosis	1+
W.B.C. 54,000	Polychromasia	3+
150 nucleated R.B.C.	Target cells	2+

*October 29, 1943.*—Child was given another transfusion, 60 c.c. Rh negative blood.

*October 30, 1943.*—Sixty-five cubic centimeters Rh citrated Rh negative blood again given into scalp vein. Prothrombin time 54 seconds Quick method, normal 12 seconds.

*November 1, 1943.*—Complete blood count showed: 10.5 = 68% hemoglobin, R.B.C. 3,500,000, 8 nucleated and W.B.C. 9,000.

There was a marked improvement noted in the child's general condition. Icterus clearing. Child was given still another blood transfusion of 60 c.c. Rh negative blood into a scalp vein. Prothrombin time 29 seconds Quick method, normal 12 seconds.

*November 3, 1943.*—Prothrombin time 19 seconds Quick method, normal 13 seconds. Normal reactions: Takes its feedings very well. Skin clear. Vitamin K (synthetic) given, twice daily during its stay in the hospital. Aqueous 1,000 units per dose (ampoule form)  $\frac{1}{2}$  c.c. injected into each arm.

*November 4, 1943.*—Blood of baby was Rh negative.

*November 8, 1943.*—On discharge baby's weight was 8 pounds 13 ounces, no icterus, blood was Rh negative. Final blood count was as follows: 12 Gm. = 78% hemoglobin, R.B.C. 3,580,000, 2 nucleated, and W.B.C. 10,500.

*Final Note.*—Infant at home and is doing well.

### Conclusions

1. Procedure for taking prothrombin time, smear and red blood count at time of delivery is recommended as a safeguard to forestall hemorrhagic disease of the newborn infant and early diagnosis of erythroblastosis fetalis.

2. Administration of water-soluble menadione in tablet or ampoule form without bile salts proves satisfactory even in obstructive jaundice. These cases will be reported in another paper now in preparation.

3. We have found that intramuscular injections work more rapidly than tablets. In cases of excessive bleeding before delivery, synthetic vitamin K clots the blood after a few hours.

4. Infants with hemorrhagic disease showed marked prolonged prothrombin time. A cord blood at birth shows a normal prothrombin time and a hypoprothrombinemia in the first three days of life. The hypoprothrombinemia and associated hemorrhages in the newborn infant were effectively prevented by the administration of  $\frac{1}{2}$  milligram water-



soluble menadione tablet to the mother, 48, 4 hours before delivery. Infants delivered from mothers without menadione are adequately protected by intramuscular injections of 1 milligram (1,000 units) within 12 hours of delivery.

5. No toxic effects noted from aquinone tablets or ampoules. There is no evidence of tissue damage in the intramuscular injection of the ampoule and it was found that the water-soluble preparation is more quickly absorbed than menadione in oil solution. This insures a more rapid response to the medication. The mothers reported a sense of smartness in the area of the injection for about five minutes and then the irritation disappears, and it is markedly less than injection of any other soluble synthetic, of which the patient really feels considerable amount of pain for at least 24 to 36 hours. There is a slight induration of the tissue which eventually disappears without any untoward effects.

6. Premature infants show a moderately prolonged prothrombin time. One of our premature infants, suffering from asphyxia, showed marked prolongation of the prothrombin time. One milligram injected intramuscularly showed a rapid rise of the prothrombin time in eight days. One premature, a bleeder, given one milligram intramuscularly, controlled the spontaneous bleeding.

7. Intramuscular injections of 1 milligram (1,000 units) cause a rapid rise of the plasma prothrombin level of newborn infants with hypoprothrombinemia whether there is hemorrhagic tendency or no clinical manifestation of the depressed prothrombin level.

The therapeutic value of water-soluble menadione is established in hypoprothrombinemia and potential or actual hemorrhage of obstructive jaundice and the hemorrhagic diathesis of the newborn infant.<sup>9</sup> It is not indicated in the various hemophilic or menorrhagic purpuras.

Hypoprothrombinemia and associated hemorrhage in the newborn infant are effectively prevented by daily oral administration to the mother during her last few weeks in pregnancy. To insure adequate protection for the infant, vitamin K, or its synthetic equivalent, should be given promptly after birth and for several days thereafter. Bleeding in hemorrhagic disease of the newborn infant is controlled within eight hours. Intramuscular injections are preferable. No toxic effects from any large doses have ever been noted.

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## A STUDY OF THE USE OF DIETHYLSTILBESTROL IN INHIBITION AND SUPPRESSION OF LACTATION

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**H**ORMONAL therapy has gained progressively wider clinical application in the past decade. In recent years such therapy has been placed on a more creditable and rational basis through the efforts of numerous workers in both experimental and clinical investigation. New fields of usefulness of endocrine therapy are being developed; and one of these is the employment of estrogens, natural and synthetic, for inhibition and suppression of lactation in puerperal women.

At the New York Lying-in Hospital, for the past ten years the routine generally adopted for the inhibition and suppression of lactation has been as follows: A tight binder is applied to the breasts and ice bags and sedatives are used to alleviate pain; fluids are restricted to 1,500 c.c. for three to four days and daily saline catharsis is urged. Ill patients, including those receiving sulfonamide therapy, apparently are not good candidates for such a routine. Such patients, in the past, frequently received no specific therapy, and it was the impression that their illnesses were unduly complicated by the additional burden, pain, and discomfort of engorged breasts. Our interest in the use of stilbestrol was stimulated by the enthusiasm of some writers and we were led to try it on a small group of patients. The results obtained in these few warranted further application of this method. As a survey of the literature failed to reveal many carefully controlled studies, we were prompted to conduct the present investigation.

### Historical Review

Since Dodds and his co-workers, in 1937 and 1938, presented stilbestrol and related compounds as therapeutic estrogens, there has been an extensive study of the drug and a rapid accumulation of reported material. A total of 1,715 clinical cases on the use of stilbestrol and its effect on lactation have been reported. In addition, well over one hundred additional cases employing testosterone and other drugs, including triphenylethylene, hexestrol and dinoestrol, have appeared in the literature. Considerable data are also available on biologic experimentation in this field.

The original investigations with synthetic preparations having estrogenic actions were made on ovariectomized rats. Of the drugs studied, 4,4' dihydroxy  $\alpha$   $\beta$  diethylstilbestrol (stilbestrol) was found to be an effective potent substance. Studies by Foley and Watson in England,

and by investigators in this country, clearly showed that lactation could be inhibited in rats by the administration of stilbestrol, as well as by estradiol or by testosterone. Further controlled animal experiments revealed changes in the pituitary glands and less distention of the mammary glands, yet with an increase of lactogenic substance in the blood titre. It would seem evident from a review of these and other studies that suppression of lactation probably is not obtained by suppression of the lactogenic hormone in the pituitary. The exact mechanism still remains unsolved.

Early clinical reports were limited in scope, and were of value chiefly in pointing out the various indications and applications of the drug. From the outset, reports were uniformly optimistic concerning the use of stilbestrol for control of lactation and breast symptoms in those cases where breast feeding was not carried out. British authors demonstrated that different results were to be expected when the drug was administered prior to the onset of lactation as compared with its administration after lactation had been established. Early reports were based on small series of cases; more recently extensive studies have appeared. Connally and his co-authors observed, along with uterine and endometrial changes, the suppression of lactation in over 70 per cent of their patients. The authors stated that none of the patients complained of engorged or painful breasts. More recently, Muekle's study of seventy-five cases revealed that on a uniform plan of medication, breast engorgement was relieved in twenty-four to thirty-six hours and that lactation was effectively controlled.

Several other articles recording fifty cases or more have been published. Clahr reported follow-up studies in a series of one hundred and twenty cases. His best results in preventing lactation were in a group of patients in whom the administration of stilbestrol was continued for more than two weeks. Where the drug was given because of engorgement, relief of pain was obtained within twenty-four hours in seventy-six per cent of cases. Stewart and Pratt, using various endocrine preparations, concluded from a detailed study that inhibition of engorgement was not synonymous with inhibition of lactation; the former was achieved in all their cases while the latter was doubtfully obtained. Abarbanel and associates studied controlled series of cases. In both control and stilbestrol treated groups nursing of the baby was continued. But little comparative advantage was noted, even in those cases receiving large daily doses of stilbestrol. Diddle and Kettel reported another controlled series. They found marked engorgement, so-called "failures," in but seven of ninety-two cases when the drug was started early; whereas, in their controls only two of seventy-five patients had no engorgement.

In summary, it is evident that stilbestrol has real therapeutic advantages. But in what particular features it can be expected to improve our care of the post-partum breast is not altogether clear. As might be expected, its use cannot obtain satisfactory results when suckling is continued. Many reports were of a general nature and based on impressions rather than on reliable statistical data. It is unfortunate, too, that differentiation was not always made between engorgement, pain, and lactation in considering the results that were obtained. Overlooked variables in clinical studies often confuse the picture and tend to vitiate

the conclusions. In all, only two investigations were carried out with control series.

### Materials and Methods

From November 1, 1942, to June 1, 1943, one hundred and ninety patients were studied in whom breast feeding was undesirable or contraindicated for one or more reasons. (Table I.)

TABLE I. INDICATIONS FOR AVOIDANCE OR DISCONTINUANCE OF LACTATION

INDICATION	NUMBER OF CASES	PERCENTAGE
Personal preference	51	33.4
Dead baby	30	19.6
Premature baby and/or twins	21	13.7
Flat or inverted nipples	12	7.5
Heart disease	10	6.5
Sick baby	6	3.9
Toxemias	5	3.3
Previous breast abscess, tumor, or mastitis	5	3.3
Puerperal infection	4	2.6
Syphilis	2	1.3
Respiratory infection	2	1.3
Pulmonary tuberculosis	2	1.3
Diabetes	1	0.6
Hyperthyroidism	1	0.6
Chicken pox	1	0.6
Total	153	99.5

The patients in whom treatment was initiated before the onset of lactation were divided into three main groups of fifty each. Patients in control group 1, designated C-1, were given no therapy whatsoever other than analgesics to relieve pain as required. Patients in control group 2, C-2, were treated with breast binders, ice bags, sedatives as indicated, restriction of fluids to 1,500 c.c. daily for three to four days and saline catharsis. Patients in the stilbestrol treated group, S-p, were given twenty milligrams of stilbestrol in divided doses according to the following schedule: 10-5-5 milligrams, each dose being separated by a twenty-four-hour period. The drug was started either on the day of delivery or the first day post partum. These patients received no other form of therapy such as binders, ice bags, etc., and there was likewise no limitation of fluids. One group of twenty-one patients, designated S-r, wherein lactation had been established and stimulated by temporary suckling, was treated with stilbestrol on the regime outlined above. Fifteen other patients who had nursed were used as a control group utilizing either no therapy or the binder routine. Four patients with nonsuppurative mastitis were treated with stilbestrol alone.

Our study endeavors to answer the following questions:

1. Is lactation inhibited when stilbestrol is administered to puerperal women prior to the onset of lactation?
2. Is breast engorgement obviated in these patients?
3. Is the pain associated with engorgement eliminated?
4. Is stilbestrol of any benefit in suppressing lactation once it is established?
5. Can stilbestrol be used with benefit in the treatment of nonsuppurative mastitis?

The results obtained in this study are based on a total of 1,888 daily examinations of patients' breasts whose babies were not allowed to nurse. A separate record covering the period of hospitalization was made for each patient. Patients who were observed less than seven days were excluded from the study. Several patients were observed for twenty-four or more days. This is particularly noteworthy in the stilbestrol group. The daily examinations were made by the authors only, and no data were drawn from nurses' notes. All notations concerning pain, engorgement, lactation and erythema were based on jointly accepted criteria. In the beginning of the study the authors checked one another's findings in order to insure uniformity of opinion.

All notations were recorded in comparative figures of from one to four plus. Pain was evaluated both by the patient's subjective complaints, and objectively by the tenderness which was elicited when the patient's breasts were palpated by the observers. Engorgement was measured by the degree of firmness of the breasts. In the event that one breast was more tense than the other, the greater degree of tension was recorded in every case. Erythema was noted according to the degree of redness and the extent of the area involved. Lactation was graded by the amount of leakage of milk in conjunction with the amount that could be expressed from the nipples by the examiner. The temperature recorded daily represented the highest registered mouth temperature for the twenty-four-hour period.

### Discussion

In this clinic we advocate breast feeding for newborn infants. However, it is not our practice to insist on breast feeding in patients who, for some reason, are strongly opposed to nursing their offspring. The indications in this study for excluding nursing are listed in Table I. We believe our indications are representative of those commonly encountered in both clinic and private practice. As it is noted, the largest group of patients included in our study was those who did not wish to nurse their babies. The next largest group was represented by those mothers who had dead born or stillborn infants; and the third group comprised those who had been delivered of premature infants and twins. It might be pointed out that no patient was urged not to nurse her baby for the purpose of this study. It is assumed that all the patients observed in our study probably would not have nursed their babies otherwise.

In the particular portion of the study devoted to the effect of stilbestrol on inhibition of lactation and freedom from pain and engorgement, there were one hundred and fifty patients. Of these 43.4 per cent were primiparas and 56.6 per cent were multiparas, the multiparas having previous nursing experience. The comparative distribution is

TABLE II. DISTRIBUTION OF PARITY IN EACH GROUP

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Primiparas	20	40	27	54	18	36
Multiparas	30	60	23	46	32	64
Total	50	100	50	100	50	100

given in Table II. History of previous nursing record was obtained in the multiparas. It was thus possible to distribute equally, in the control and stilbestrol prescribed groups, those patients in whom adequate lactation could be expected, and thereby minimize this one variable when comparing results of the study.

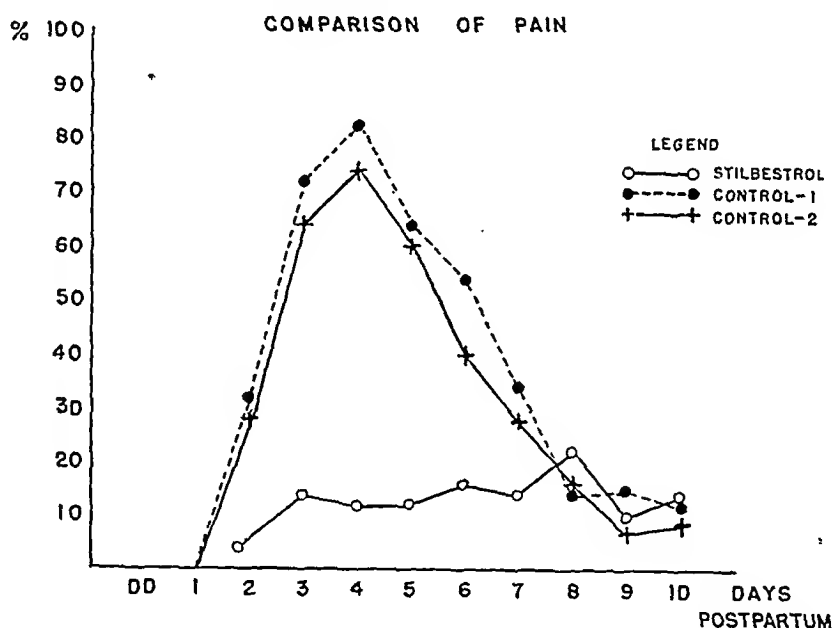


Chart 1.—Comparison of total number of patients with breast pain of all degrees in stilbestrol treated patients (S-p), control group with no therapy (C-1), and control group with conventional treatment (C-2).

Chart 1 demonstrates the percentage incidence of breast pain as it occurred in each of the three groups. The degree of pain varied and clinically was measured as ranging from one plus to four plus in intensity. Pain occurred on the fourth day in 82 per cent of the control group, C-1, that had no treatment; by the tenth day only 10 per cent in this group complained of pain. A similar incidence was recorded in the control group, C-2, receiving conventional treatment; the maximum incidence was only 8 per cent below that of the former. Thus, from a study of this graph, conventional treatment appears to obtain only slightly better results. Contrastingly, the occurrence of pain in the group treated with stilbestrol, S-p, was strikingly low.

Further analysis of each group was made in order to compare the degree and intensity of breast pain. Chart 2 reveals that pain in the

group treated with stilbestrol was, for the most part, of minor intensity, particularly in the latter days. Charts 3 and 4, on the other hand, show that from 30 to 40 per cent of the pain developed, in control groups, was of relatively intense character.

A comparison of the total number of patients with breast engorgement is shown in Chart 5. One notes that from 90 to 94 per cent of the patients in both control series had engorged breasts. This maximum en-

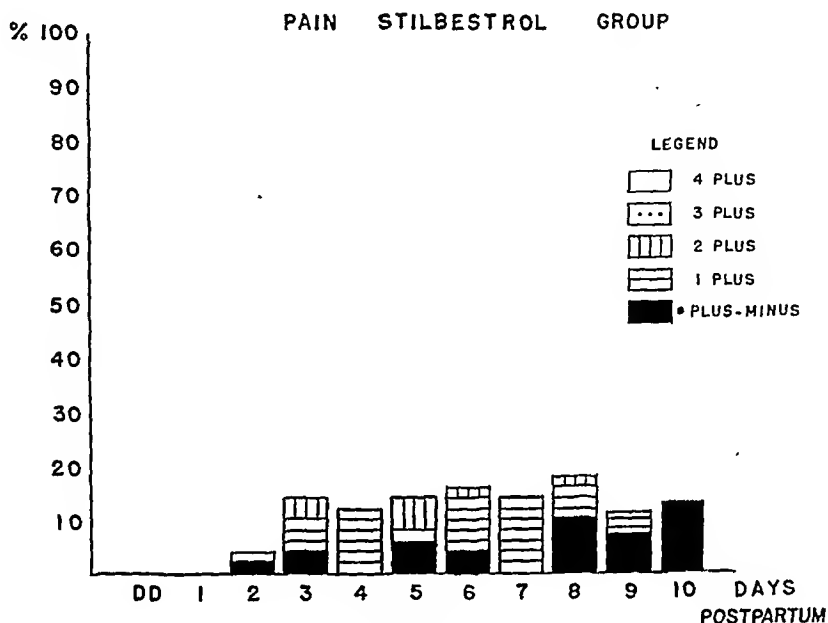


Chart 2.

Charts 2, 3 and 4.—Occurrence of breast pain, graphed according to degree of intensity from plus-minus to four plus, in each of the study groups.

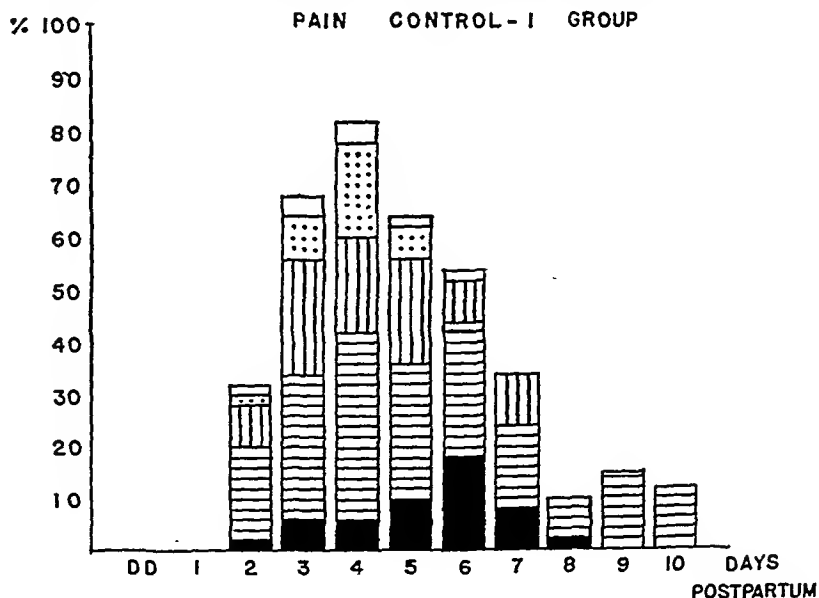


Chart 3.—For legend see above.

gorgement is evident on the fourth and fifth post-partum days, then rapidly declines to one-fourth of this value by the tenth day. Patients on stilbestrol therapy in comparison, were relatively free of engorgement. Breast congestion in this group, while delayed in some instances, at no time occurred in over 37 per cent of the cases. Furthermore, the breast tension was observed to be of shorter duration than in the control series.

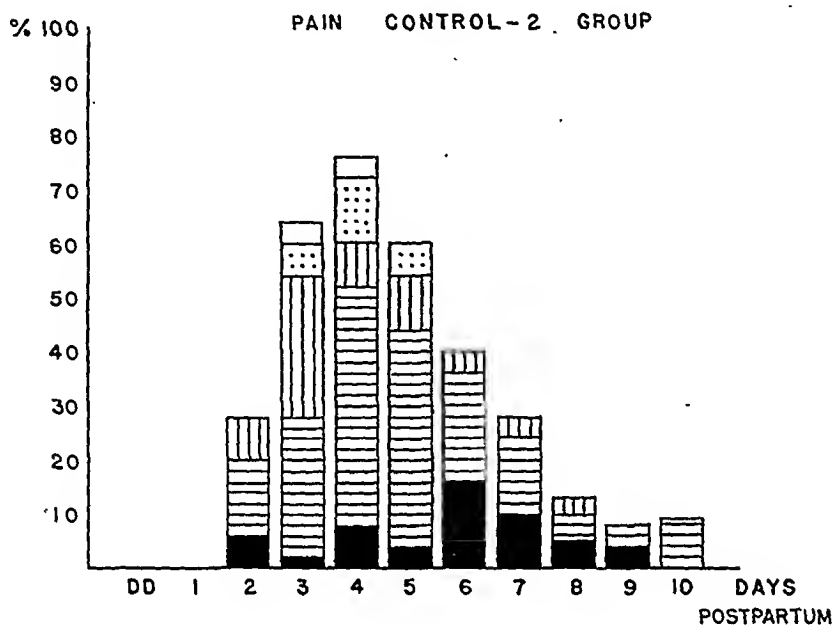


Chart 4.—For legend see opposite page.

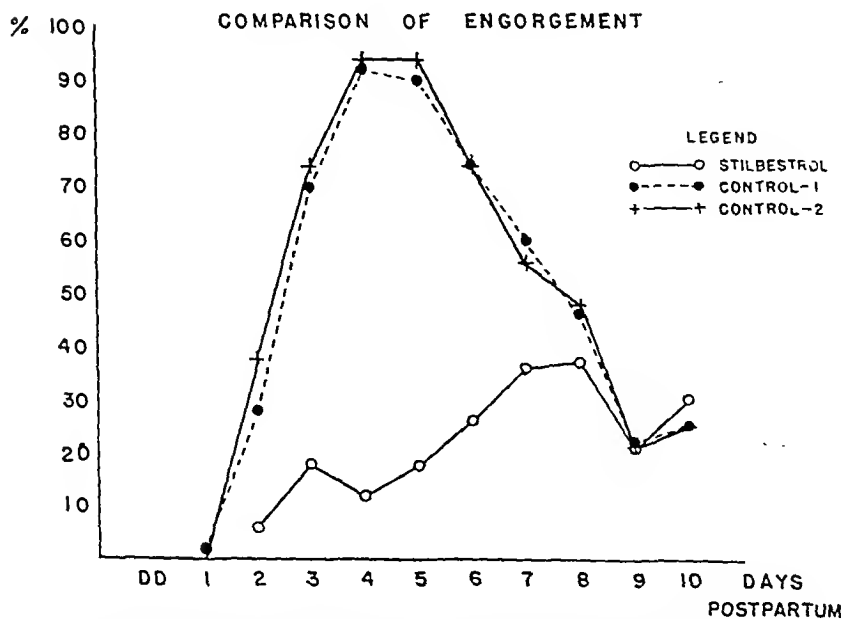
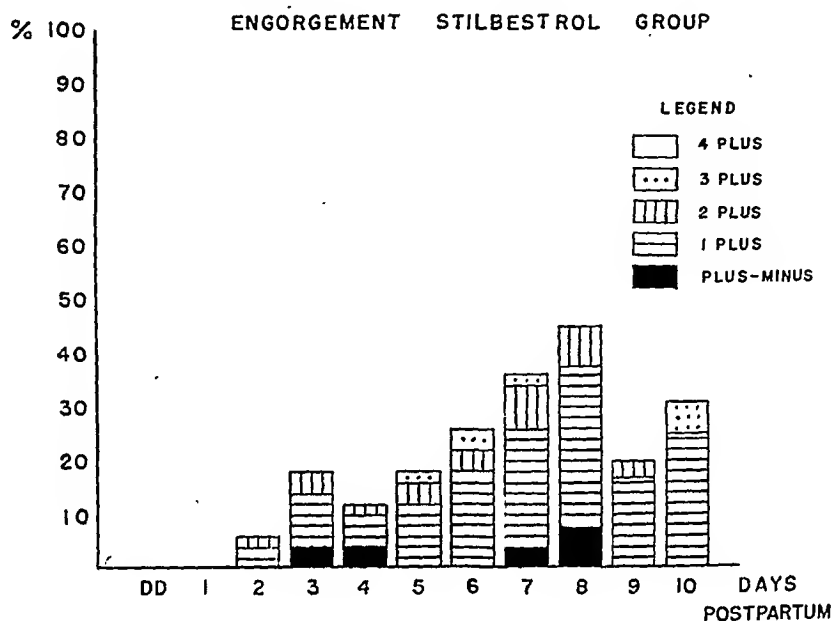


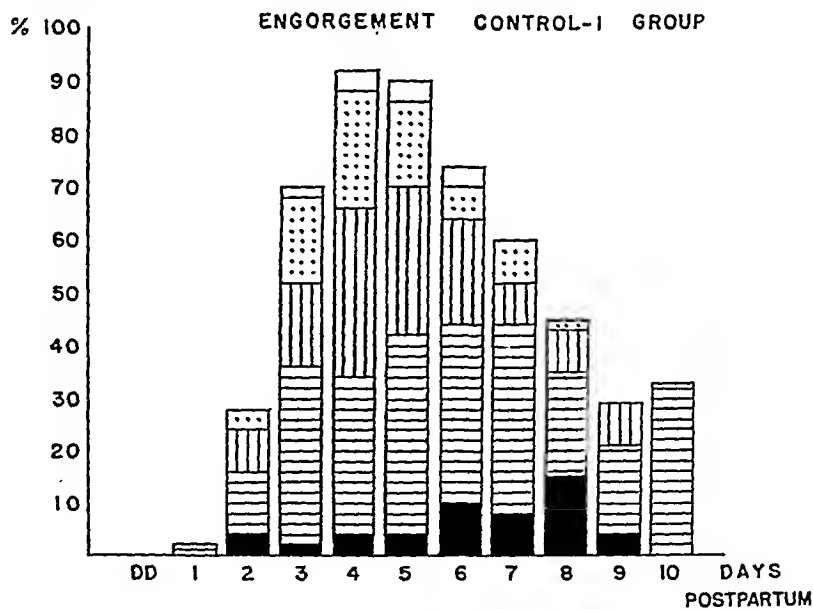
Chart 5.—Comparison of total number of patients with breast engorgement of all degrees in stilbestrol treated patients (S-p), in control group with no therapy (C-1), and in control group with conventional treatment (C-2).



Charts 6, 7 and 8 contrast the relationship of the degree of the intensity of engorgement to its occurrence in the puerperium in each of the three groups. Engorgement in the stilbestrol treated group is shown to be of moderate to mild degree throughout. In the control group receiving no treatment, breast congestion was found to be somewhat more intense. Studying the third series treated by conventional measures, there is noted a close similarity of moderate and severe engorgement to that of the second series.



Charts 6, 7 and 8.—Occurrence of breast engorgement, graphed according to degree of intensity, from plus-minus to four plus, in each of the study groups.



Lactation in each of the three classes studied is compared in Chart 9. The stilbestrol treated group exhibited a relatively low curve of lactation reaching a peak of 43 per cent on the eighth day. While in the control group omitting treatment, a high value of 88 per cent of patients was found to be lactating on the fifth day, the incidence then rapidly dropping off. A similar response, though less marked, was exhibited by the last group receiving conventional treatment; more mothers lactated

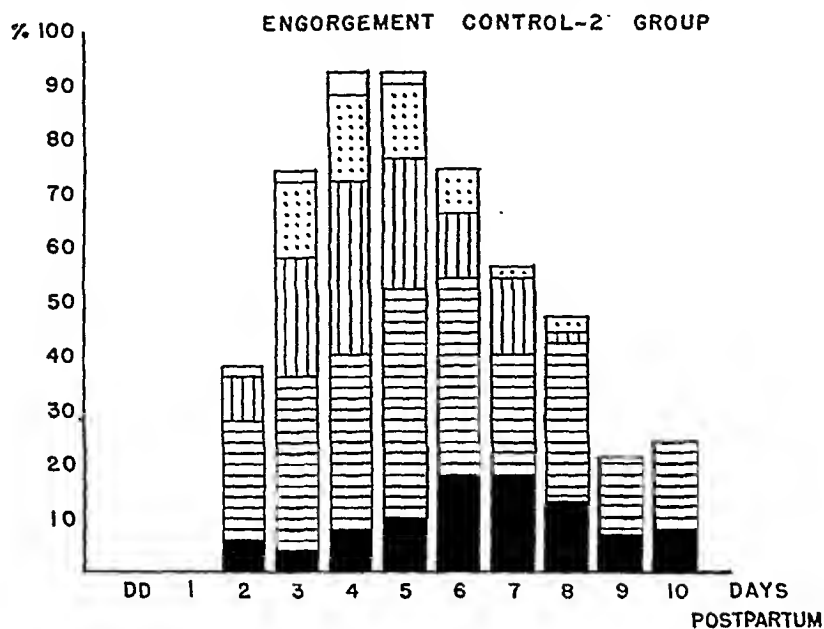


Chart 8.—For legend see opposite page.

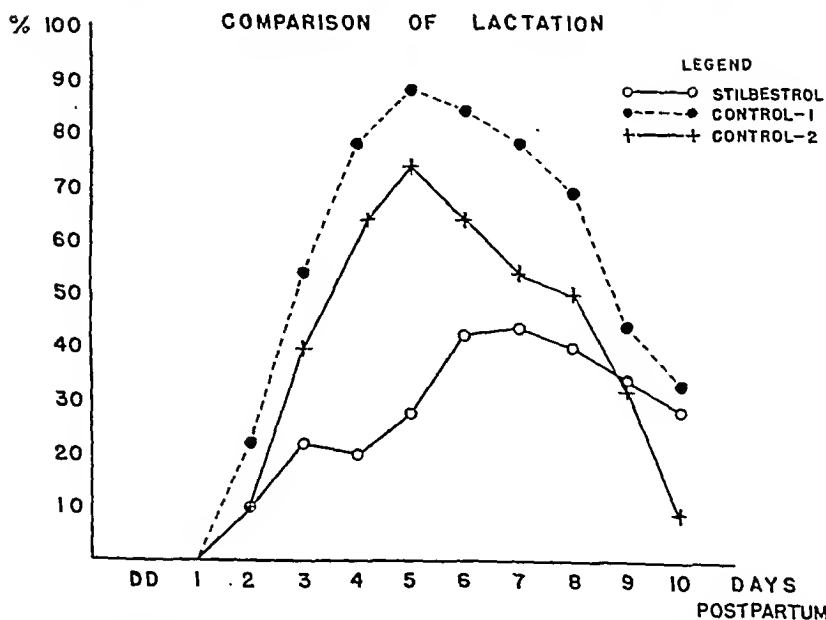


Chart 9.—Comparison of total number of patients with lactation of all degrees in stilbestrol treated patients (S-p), in control group with no therapy (C-1), and in control group with conventional treatment (C-2).

again on the fifth day, followed by a sharp decline. In this chart are recorded curves similar to those of engorgement recorded in Chart 5 with a rise and fall of engorgement approximating rise and fall of lactation. So, for example, in stilbestrol treated cases, a complementary late rise of lactation is seen with a late transient rise in breast engorgement. Further study of these charts reveals the equal efficacy of stilbestrol in partially preventing breast engorgement and lactation.

The degree of lactation in each series was studied and compared in Charts 10, 11 and 12. It may be thus further observed that patients

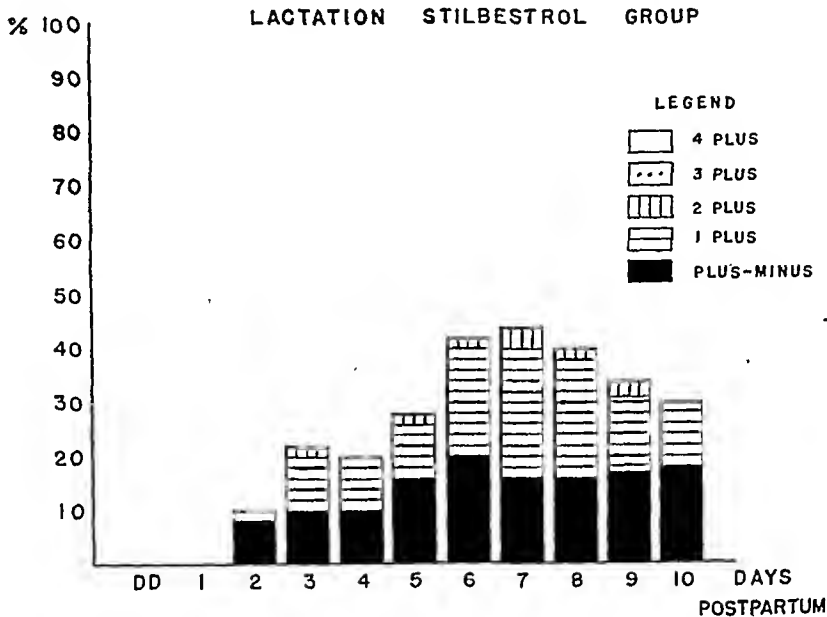


Chart 10.

Charts 10, 11 and 12.—Occurrence of lactation, graphed according to degree, from plus-minus to four plus, in each of the study groups.

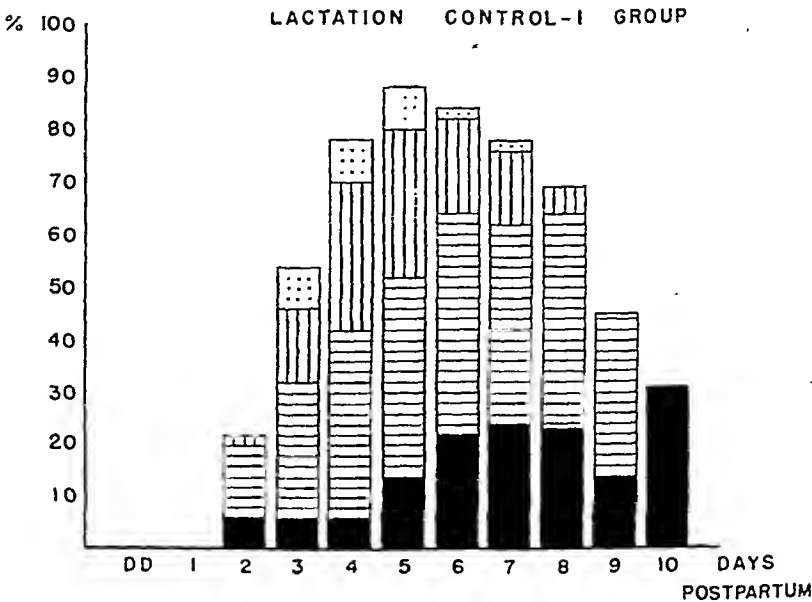


Chart 11.—For legend see above.

in both control series exhibited a greater degree of lactation, particularly those without treatment, than in the stilbestrol treated series. In other words, not only were there fewer cases of lactation in the stilbestrol treated patients, but of those lactating, the degree was noticeably less marked.

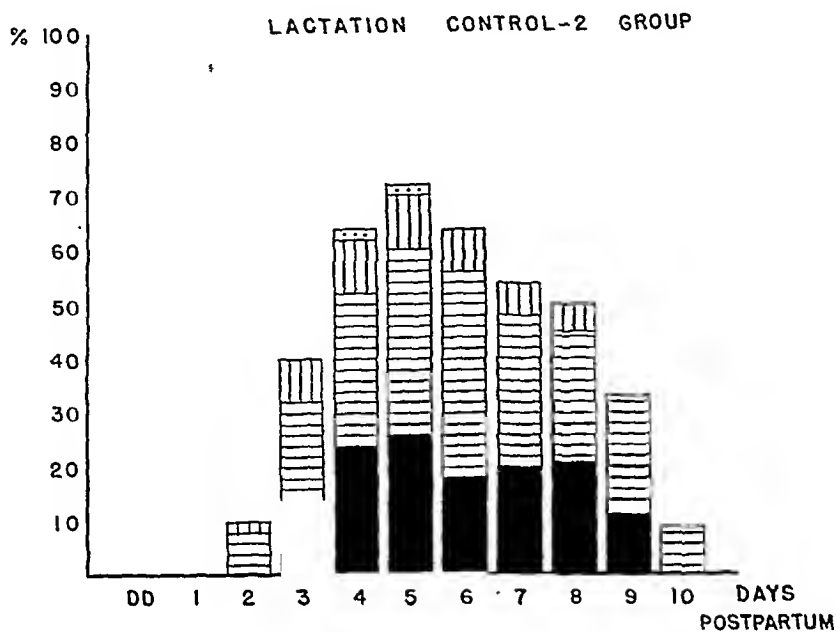


Chart 12.—For legend see opposite page.

The occurrence of erythema in all our patients was minimal. This complication was present in 4 per cent of the stilbestrol treated cases, in 14 per cent of the control cases omitting treatment, and in 8 per cent of the control cases on conventional prophylactic measures. Combining the two control groups, an average figure of 11 per cent was found to be almost three times the incidence in the stilbestrol group. Yet in none of these cases was the erythema severe, nor did it accompany the other classical features indicative of mastitis.

As noted above, the highest daily temperature was recorded on our study sheet. These temperature elevations were in turn correlated with breast engorgement, with one-day fevers, and with morbidity due to all causes. In view of the diversity of opinion regarding the occurrence of fever due to engorgement, we use the term "breast morbidity" where there is an elevation in temperature to  $38.0^{\circ}\text{C}$ ., or more on any two days, associated with breast engorgement, and where there is no other explanation for the fever. "Engorgement with fever" represents a single day fever coincident with breast engorgement. Total morbidity is that puerperal morbidity due to all causes. In Table III is listed the occurrence of each in the three study groups. Single day fevers associated with engorged breasts occurred in equal frequency in each group. Actual "breast morbidity" was negligible. Total morbidity of the one hundred and fifty patients in this study was essentially that of the clinic as a whole, namely, 10 per cent.

Analyzing our figures from the viewpoint of onset of pain, engorgement and lactation, we find, as has been the general impression, that in

TABLE III. OCCURRENCE OF POST-PARTUM FEVER AND MORBIDITY IN 150 CASES

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Total Cases	50	100	50	100	50	100
Engorgement with fever	4	8	5	10	5	10
Breast mor- bidity	0	0	1	2	2	4
Total morbidity	8	16	4	8	3	6

Average total morbidity 150 cases = 10%

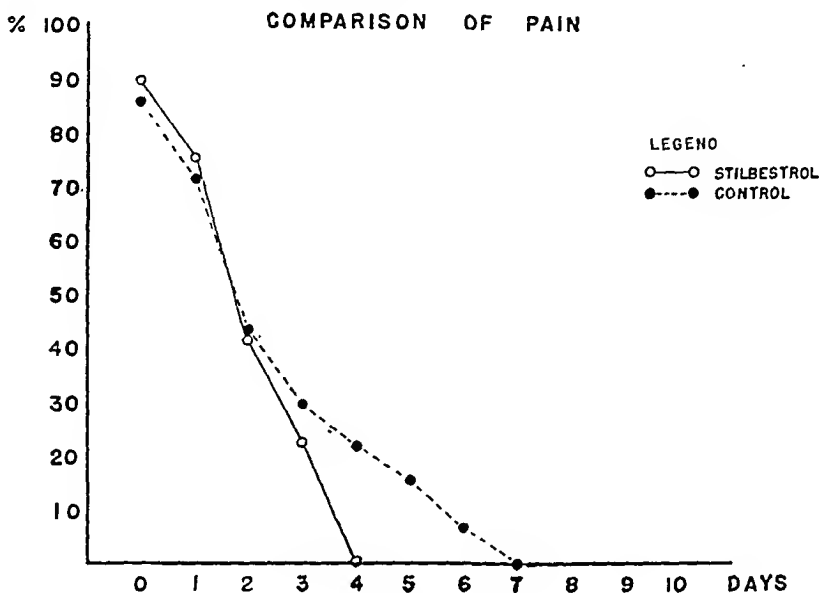


Chart 13.

Charts 13, 14 and 15.—Comparison is made of the number of days required for the subsidence of pain, engorgement, and lactation; the stilbestrol treated groups (S) in contrast to the control groups (C).

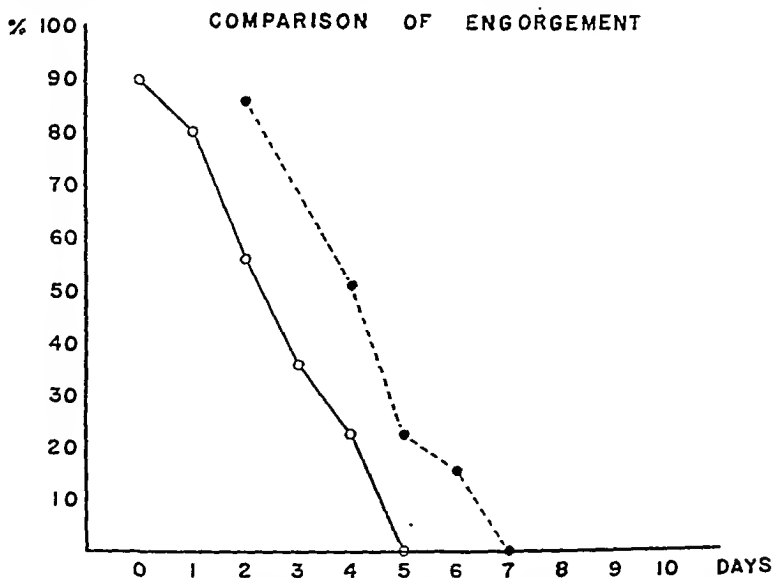


Chart 14.—For legend see above.

all the control cases the average day of onset was the third post-partum day. It may be pointed out again that our stilbestrol treated patients demonstrated an average delay of three days; that is, breast symptoms and related findings developed on the sixth day.

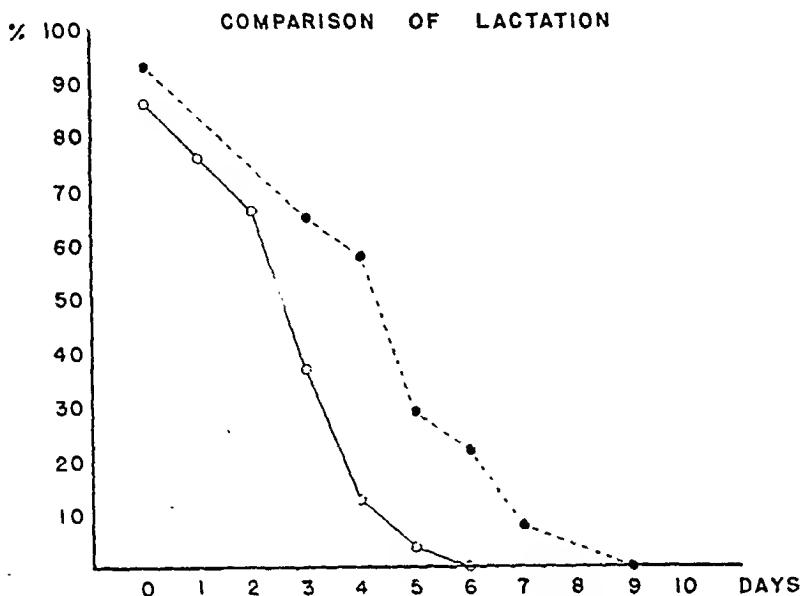


Chart 15.—For legend see opposite page.

TABLE IV. FREEDOM FROM PAIN, ENGORGEMENT, AND LACTATION IN 150 CASES

	STILBESTROL		CONTROL-1		CONTROL-2	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Total Cases	50	100	50	100	50	100
Patients with no pain	23	46	2	4	0	0
Patients with no engorgement	20	40	3	6	0	0
Patients with no lactation	13	26	1	2	7	14

Table IV reveals, in a striking manner, the efficacy of stilbestrol therapy. In the control-1 group, over the entire post-partum hospital course, only 4 per cent of patients was free of pain, and only 6 per cent was free of engorgement; there were none in the control-2 group; while in the stilbestrol group approximately two out of every five individuals were entirely free of pain and free of engorgement. As might be expected, the freedom from lactation in this latter group, though less marked, was significantly better when compared with controls.

A smaller series of cases was studied, again with accompanying control series, to determine the suppressing effect of stilbestrol in cases where lactation had been established. In Chart 13 is recorded the number of days to relief of pain. Patients receiving stilbestrol were entirely relieved of pain within four days. A similar decrease of pain is noted in control groups, save that in a few instances pain persisted until the seventh day. Engorgement was studied and, noted in Chart 14, was

found to subside more rapidly by approximately two days in the stilbestrol treated cases than in the control cases. Chart 15 portrays a similar and rapid decline in lactation. By the sixth day, in the stilbestrol treated patients all lactation had ceased; by the ninth day this was likewise true of the comparative control group. Where nursing and/or lactation had been established, we can thus point out that administration of stilbestrol has a definite though limited value in hastening the subsidence of annoying features of pain, engorgement, and lactation.

In this study only three cases of breast fever were recorded, one in the stilbestrol treated group and two in the controls, too few for proper differential evaluation. So also only six cases of erythema were found, three each in the stilbestrol treated and in the control series.

During the course of this seven-month study period, we unfortunately were able to treat with stilbestrol only a few cases of mastitis over a period adequate for analysis. It is our impression from this limited experience with stilbestrol, comparing results with those attained using conventional measures, that the former probably has little beneficial effect in the treatment of mastitis. While we are, as yet, in no position to express a final opinion, we would not recommend the drug, save as an adjuvant, in the treatment of mastitis.

A final commentary may be mentioned. In no case of administration of stilbestrol did we observe nausea or vomiting, or other evidence of sensitivity to the drug. This observation is in agreement with similar reports in the literature. Like others, we have no real explanation for this peculiar immunity.

### Summary

One hundred and ninety patients, including comparative control groups, who did not nurse or in whom nursing was discontinued, were studied to determine the therapeutic effect of stilbestrol on breast pain, engorgement, lactation and erythema. Patients were evenly distributed on the basis of previous nursing record. Separate studies were carried out on patients where lactation had been established and on those selected prior to the onset of lactation. In all, 1,888 separate daily examinations were carried out by the authors.

### Conclusions

1. Stilbestrol, by comparison, was found highly effective in preventing the development and minimizing the intensity of breast pain.
2. Engorgement was reduced in incidence, in the stilbestrol group, to one-third that of the controls; it was less intense, and developed later in the puerperium.
3. Lactation, while frequently delayed in onset, was definitely, though less markedly, depressed than were the other features studied.
4. Erythema was found in but one-third the number of stilbestrol treated cases, compared with controls.

5. Fevers associated with breast engorgement occurred in approximately the same number of cases in each study group.

6. Entire freedom from breast pain and engorgement in the stilbestrol treated series was striking in contrast with the control series.

7. Conventional therapeutic measures were found, comparing results in the two control groups, to be of little benefit save in the partial reduction of lactation.

8. Separate control studies on the therapeutic effect of stilbestrol once lactation had been established showed that the treatment held but slight advantage in the relief of breast pain; that relief from engorgement and subsidence of lactation was definitely, though not markedly, bettered.

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# THE ABSORPTION OF STEROID HORMONES FROM THE ORAL MUCOUS MEMBRANES, WITH SPECIAL REFERENCE TO THE SUBLINGUAL ADMINISTRATION OF PROGESTERONE

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IN THE search for more convenient modes of administration of the steroid hormones, attention has been directed in recent years to the absorptive capacity of the oral mucous membranes. Freudenberger and Howard<sup>1</sup> were the first to call attention to this route for steroid hormones when they found that pregnancy urine dropped in the mouths of immature rats, caused premature opening of the vagina. Since the amount retained in the mouth was scarcely more than the amount necessary to moisten its lining, they concluded that the active principle in pregnancy urine was absorbed through the oral mucous membranes. Looking back upon this experiment, it seems possible that what was absorbed was chorionic gonadotropic hormone, rather than estrogen; but in any case the observation was sufficient to call attention to the possibility of absorption of the steroid hormones directly from the oral cavity.

## Estrogens

Gysi<sup>2</sup> and Engels,<sup>3</sup> as cited by Miescher and Gasche,<sup>4</sup> and Salmon and Geist<sup>5</sup> were the first to apply this method clinically. Salmon and Geist, using a solution of  $\alpha$ -estradiol in propylene glycol, were able to produce vaginal cornification in 8 estrogen-deficient women with daily doses of 0.2 to 0.3 mg. for 7 days. Herrnberger<sup>6</sup> and Reifferschied and Schmidt<sup>7</sup> used alcoholic solutions of estradiol to obtain endometrial proliferation in menopausal and amenorrheic women with doses ranging from 6 to 15 mg. per day for 6 to 20 days. Giesen<sup>8</sup> obtained similar results with tablets allowed to dissolve under the tongue. Albers<sup>9</sup> reported that when estradiol was administered sublingually, twice the intramuscular dose was required to produce equal lowering of the serum calcium. Joël<sup>10</sup> was able to produce endometrial proliferation in women who had received previous x-ray therapy with 4 to 6 mg. daily for 15 days in the form of sublingual tablets. Hall<sup>11</sup> reported vaginal cornification in menopausal women with doses of estradiol benzoate in propylene glycol of 0.2 mg. daily for 10 to 14 days (totaling 2.0 to 2.8 mg.) as compared with a total of 1.666 mg. given by injection in two doses 5 to 7 days apart. Forty-one per cent of his patients showed relief of symptoms or improvement with this dose and route of administration, to the same degree as after administration by injection, while 58 per cent showed slight recurrence of symptoms. He concluded that with equal doses the results would have been equal, but that individualization of doses is necessary. Diddle, Nagyfy, and Sells<sup>12</sup> found that with frequent sublingual administration  $\alpha$ -estradiol is as effective in the suppression of lactation as by injection.

Hohlweg (cited by Giesen<sup>8</sup>) found that a sublingual dose of estradiol 35 to 45 times the subcutaneous dose and 1/10 of the oral dose produced

estrus in castrated rats. Reifferschied and Schmidt<sup>7</sup> reported the sublingual dose in rats to be  $\frac{1}{6}$  the oral dose of estradiol glucoside and  $\frac{1}{3}$  that of estradiol. Miescher and Gasche<sup>4</sup> found that the effective dose of an alcoholic solution placed under the tongue was  $\frac{1}{10}$  to  $\frac{1}{20}$  of that by stomach tube when measured by the increase in weight of the uterus in castrated rats. This dose they state is nearly equal to the dose by injection or by inunction. Further they maintain that division of doses has little or no effect.

Castrodale, Loeffel, and MacBryde<sup>13</sup> reported that diethylstilbestrol in propylene glycol solution relieved menopausal symptoms in 11 out of 17 patients in the same dose as that effective orally, or by the gastrointestinal route; that is to say, about twice the intramuscular dose. One patient indeed had greater relief with the sublingual than with other forms of medication.

It would seem that, with the exception of Hohlweg's report cited by Giesen,<sup>8</sup> whenever a comparison of the minimal effective dose has been made estrogens and stilbestrol are found to be about equally effective by sublingual administration as by injection. It should be also noted that the dose may vary from one individual to another.

### Desoxycorticosterone

Anderson, Haymaker, and Henderson,<sup>14</sup> Anderson and Haymaker,<sup>15</sup> and Turnoff and Rowntree<sup>16</sup> maintained patients with Addison's disease on desoxycorticosterone acetate in propylene glycol solution containing 20 per cent alcohol, with doses usually less than twice the intramuscular dose. Thorn, Greif, Coutinho, and Eisenberg,<sup>17</sup> using the hormone in pure propylene glycol, found that their patients required at least 3 times as much sublingually as intramuscularly. In 1942 Thorn, Dorrance, and Day<sup>18</sup> reported that the dose of sublingual tablets and solutions was 6 to 8 mg. daily as compared to 2 mg. intramuscularly and to a calculated dosage of 1.2 mg. daily for implanted pellets. Clinton and Thorn<sup>19</sup> reported only slight rises in plasma volume in normal subjects given sublingual tablets, whereas significant increases were obtained by injection of comparable amounts of the hormone. Wilson,<sup>20</sup> using  $1\frac{1}{2}$  to 7 times the intramuscular dose in 4 patients, reported return of what he felt were insufficiency symptoms in 3 patients. The fourth patient, the only one on the lowest dose, died of an intercurrent infection during treatment. Under these conditions the requirement for desoxycorticosterone is known to increase. In the others the symptoms may have been due to the large overdoses used, for as Engel, Cohn, and Soffer<sup>21</sup> mention, overdosage of desoxycorticosterone is often associated with symptoms difficult to distinguish from incipient adrenal insufficiency. These authors tried the sublingual method on 5 patients and were able to maintain 2 patients with extremely mild adrenal insufficiency on doses no larger than the intramuscular dose. Two patients could not be maintained at this level. One patient developed incipient insufficiency symptoms on twice the injection dose. The sublingual doses, however, were apparently not divided into 4 or 5 per day as recommended by the other authors. According to Schachter,<sup>22</sup> Thaddeus<sup>23</sup> and Heni<sup>24</sup> in Germany have reported agreement with the results of Anderson and Haymaker. Thorn et al.<sup>17</sup> reported a 3 to 1 ratio of sublingual to intramuscular dosage in adrenalectomized dogs. Cleghorn, Clarke and Greenwood<sup>25</sup>

were unable to maintain adrenalectomized dogs on doses as high as 4 times the standard intramuscular dose, but they admitted that adequate precautions to prevent swallowing of the medication were not used.

It would seem then that with the exception of Wilson's somewhat questionable results, it is possible to maintain mild cases of adrenal insufficiency on doses from the same to twice the intramuscular dose. For more severe cases doses from 3 to 4 times the intramuscular dose are needed. Again there seems to be individual variation in the dose needed.

It has been pointed out (Henderson, personal communication) that the quantitatively different results obtained by some of the workers, namely Anderson, Haymaker, and Henderson on one hand, and Thorn and co-workers on the other, may have depended on a difference in the absorption of the hormone solution. Thorn et al. dissolved the desoxycorticosterone in pure propylene glycol, having a surface tension of 42 dynes per square centimeter, whereas Anderson, Haymaker, and Henderson used propylene glycol diluted with 20 per cent absolute alcohol, a mixture which has a surface tension of only 31 dynes per square centimeter and which therefore would be more readily absorbed.

### Androgens

Joël<sup>26</sup> used sublingual methyl testosterone tablets for the relief of menopausal symptoms in women in doses ranging from 5 to 30 mg. daily. Spence<sup>27</sup> reported maintenance of potency in a male castrate with sublingual methyl testosterone tablets on a dose 4 times the injection dose. Lisser, Esemilla, and Curtis<sup>28</sup> compared the efficacy of sublingual methyl testosterone, testosterone propionate, and testosterone in propylene glycol. In 4 sexually retarded cryptorchid males, they were able to establish sexual maturity with  $\frac{1}{3}$  the oral dose or about  $1\frac{1}{2}$  times the intramuscular dose. In 5 eunuchs the effective sublingual dose was equal to 3 times the injection dose. Testosterone was more effective at a given small dose than were its esters. Miescher and Gasche,<sup>29</sup> however, found that in castrate rats methyl testosterone was 3 times more effective than testosterone when administered sublingually. They also reported that as with the estrogens division of doses was not important.

From these experiments it appears that average effective dose of the androgens administered sublingually is about 3 times the intramuscular dose. Hurxthal<sup>30</sup> reported more recently that for maintenance purposes in eunuchoid patients, sublingual administration of testosterone in propylene glycol compares favorably with intramuscular injection of the same compound in oil, in some cases but not in others. About 3 times as much is needed as by pellet implantation. Again it will be seen that there is more individual variation with the sublingual route of therapy.

### Pregneninolone

Joël<sup>30</sup> was able to produce bleeding in patients previously treated with sublingual estrogens with sublingual tablets of pregneninolone in doses  $3\frac{1}{2}$  times the intramuscular dose of progesterone.

In general, all these experiments suggest that with the exception of the estrogens, which appear to be equally potent sublingually, the average sublingual dose of the steroid hormones is 3 to 4 times the intramuscular dose. In all, there seems to be considerable individual variation as to the effective dose. Furthermore, it seems best to split the dosage into 4 to 5 small doses a day.

### Progesterone: Experiments and Results

In order to test the efficacy of the sublingual administration of progesterone, the present author carried out hormone assays on rabbits and on Rhesus monkeys. Solutions of crystalline progesterone in propylene glycol containing 20 per cent absolute alcohol (such that the concentration of the hormone was 10 to 20 mg. per c.c.) were used as the test substance.

TABLE I. PRODUCTION OF PROGESTATIONAL ENDOMETRIUM IN THE RABBIT BY ADMINISTRATION OF PROGESTERONE IN PROPYLENE GLYCOL

MODE OF ADMINISTRATION	TOTAL DOSE	ENDOMETRIAL RESPONSE
Subcutaneous	0.5 mg.	+++
		+++
		+++
		++++
		++++
Subcutaneous	1.0 mg.	++
		+++
		++++
		++++
		++++
Sublingual	1.0 mg.	0
		0
		0
		0
		+
Sublingual	2.0 mg.	++
		++
		+++
		++++
		++++
Sublingual	3.0 mg.	+
		+
		++
		++
		++++
Sublingual	4.0 mg.	++
		++
		++
		++
		+++
Sublingual	8.0 mg.	+
		++
		++
		++
		+++

*Rabbits.*—In this series of experiments the efficacy of sublingual and subcutaneous administration of progesterone in propylene glycol was compared. Thirty-five assays for progesterone were done on mature

virgin female rabbits according to the standard method described by Corner and Allen.<sup>31</sup> The progesterone-propylene glycol solution was diluted to concentrations of from 0.5 mg. to 8 mg. per c.c. with propylene glycol containing 20 per cent absolute alcohol, and administered 3 times daily for 5 days. For sublingual use, the solution was administered in doses of 1/16 c.c. from a tuberculin syringe fitted with a blunt 18 gauge needle by inserting the tip of the needle under the tongue and injecting the full dose at one time. The amount of solution given subcutaneously was also 1/16 c.c.

As may be seen from Table I, the amount of endometrial response to progesterone given sublingually was extremely variable, except with the smallest dose (total 1 mg. in 5 days), which was almost uniformly ineffective; in only one instance was even the slightest response elicited. When administered subcutaneously, however, a full response could be produced fairly regularly with 0.5 mg. A nearly full response could be obtained from time to time on all sublingual doses from 2 to 8 mg. In this small series, however, the best response was obtained with the 2 mg. dose.

It must be admitted that the technique of administration employed with the rabbits did not involve as great protection against swallowing of the dose or loss of a portion of the dose from the mouth as the technique employed with the monkeys (see *infra*). The presence of slight variation in the response even with the subcutaneous route, however, tends to support the belief that progesterone in this type of solution (designed for rapid absorption) produces variable results; for when administered subcutaneously in oil (a medium designed for slow continuous absorption), the response is more constant (Corner<sup>32</sup>).

The full response obtained with subcutaneous administration of a total of 0.5 mg., given 3 times daily, agrees favorably with the statement of Pineus (cited by Corner<sup>32</sup>) that by giving progesterone in oil twice daily the minimal effective dose can be reduced to 0.67 mg. When administered subcutaneously, therefore, progesterone is apparently at least as effective in propylene glycol solution as in oil solution. On the other hand, about 4 times the subcutaneous dose is required if the drug is given sublingually, and the response becomes extremely variable.

*Monkeys.*—The animals employed were 5 adult female Rhesus monkeys which had gone through one or more menstrual cycles before being castrated. The technique of assay was that used by Corner<sup>33</sup> in determining the minimal effective dose of progesterone administered subcutaneously. In his determination the animals were primed for 10 days with 125 International Units of estrogen subcutaneously daily. When sufficient progesterone was then given, bleeding did not occur until 3 to 8 days after withdrawal of the hormone. The minimal dose required to protect all animals from estrogen-deprivation bleeding was found to be 0.5 mg. daily.

In the present experiments, after 10 to 12 days' priming with estrogen,\* progesterone was administered sublingually daily for 10 days by the following technique. The mouth was pried open with the tongue retracted, and the solution dropped into the sublingual space on opposite sides of the frenum. The animal was not released until after the solution disappeared or the floor of the mouth filled with saliva (usually about 15 seconds). No active swallowing movements were noted imme-

\*Used in the form of Amniotin (Squibb).

diately. Since the solution employed has a surface tension of only 32 dynes per sq. cm., absorption probably took place before any of the material could be swallowed. The dose, varying from 0.05 to 0.1 c.c. (0.5 to 2 mg. of progesterone), was administered from a tuberculin syringe fitted with a blunt 18 gauge needle which delivered 4 drops per 0.05 c.c. It was found impracticable for technical reasons to give the solution more than twice daily.

In all, 12 trials with the 5 animals were made. As will be seen from Table II, bleeding was inhibited in two animals (182, 147) with 1 mg. daily. Number 182 could be prevented from bleeding when the dose was given once daily. Since No. 147 bled earlier than usual after the withdrawal when 2 daily doses were given, it is felt that the divided dose of 1 mg. represents the minimum effective dose for this animal and that bleeding would not have been inhibited with a single daily dose. When No. 147 was given 2 mg. in 2 daily doses, bleeding following withdrawal of progesterone occurred within the usual limits. In No. 183, 2 mg. given once daily was followed by bleeding on the fifth day of treatment, while 2 mg. in divided doses prevented bleeding until the eighth or ninth day in each of 3 trials. This result was interpreted as indicating that the 2 mg. dose thus divided was very near to the minimal effective dose for this animal. Further division of the 2 mg. dose might have inhibited bleeding in this animal.

TABLE II. INHIBITION OF ESTROGEN-DEPRIVATION BLEEDING BY SUBLINGUAL ADMINISTRATION OF PROGESTERONE TO THE RHESUS MONKEY

ANIMAL	TOTAL DAILY DOSE	SIZE OF EACH DOSE	BLEEDING DURING ADMINISTRATION OF PROGESTERONE	BLEEDING AFTER DISCONTINUING PROGESTERONE
182	1 mg.	1.0 mg. (0.1 c.c.)	Inhibited	Fourth day
678	1 mg.	1.0 mg. (0.1 c.c.)	Sixth day	
182	1 mg.	0.5 mg. (0.05 c.c.)	Inhibited	Fourth day
147	1 mg.	0.5 mg. (0.05 c.c.)	Inhibited	Second day
184	1 mg.	0.5 mg. (0.05 c.c.)	Fifth day	
183	2 mg.	1.0 mg. (0.10 c.c.)	Fifth day	
147	2 mg.	1.0 mg. (0.05 c.c.)	Inhibited	Eighth day
147	2 mg.	1.0 mg. (0.05 c.c.)	Inhibited	Third day
183	2 mg.	1.0 mg. (0.05 c.c.)	Ninth day	
183	2 mg.	1.0 mg. (0.05 c.c.)	Eighth day	
183	2 mg.	1.0 mg. (0.05 c.c.)	Eighth day	
184	4 mg.	2.0 mg. (0.10 c.c.)	Fourth day	

These experiments, as far as they go, suggest that in the Rhesus monkey the ratio between the minimal effective dose sublingually to intramuscularly is of the order of 4 or 5 to 1. Certainly 1 mg. and 2 mg. sublingually do not produce as uniform results in the prevention of estrin-deprivation bleeding as do  $\frac{1}{2}$  mg. and 1 mg. administered subcutaneously in oil, as in the experiments of Corner.<sup>33</sup> Experiments on one animal tend to support the belief that giving the total daily dose in several small doses decreases the required minimum effective dose.

### Discussion

During the past three years the search for more convenient modes of administering steroid hormones has led to numerous investigations of the possibilities of sublingual administration. From these chiefly clinical reports certain facts concerning this route have become evident. (1) In

order to obtain maximum efficiency, the daily dose should be given in at least 5 or 6 small doses. (2) The size of the effective dose is more variable than by other methods of administration. (3) The size of the effective dose varies with the hormone administered. Estrogens are nearly, if not equally, as effective sublingually as intramuscularly. With the other steroid hormones the sublingual dose is at least 4 times the intramuscular dose. In the case of testosterone, the pure hormone is somewhat more effective than any of its esters. (4) There is no evidence that the tablet form is any more efficient than the solution form except in the matter of convenience to the patient.

The testing of the sublingual method of administration on animals presents many difficulties. One cannot expect them to inhibit swallowing movements, much less hold the mouth open with the sublingual space exposed while the solution is dropped into the mouth. With the Rhesus monkeys it proved impracticable to catch them for administration more than twice daily. Finally, one has to take into consideration a possibly lower capacity for absorption on the part of the oral mucous membrane in the smaller mammals, such as the rabbit.

In spite of the difficulties involved, these experiments are offered as a suggestion that with sublingual administration of progesterone amounts in the order of 4 times the intramuscular dose are required. This result is in the same range as the results reported for other steroid hormones, with the exception of the estrogens.

In rabbits and Rhesus monkeys, however, sublingual administration of progesterone, because of the extremely variable response encountered and the larger doses required, seems to be unsatisfactory. Results reported in the literature for other steroid hormones administered sublingually in humans show more uniform response. It is possible, therefore, that sublingual administration of progesterone in human subjects may prove more reliable than it is in animals.

### Summary

1. A review of the literature on sublingual administration of the steroid hormones in various solvents and in tablets is presented. The conclusion is offered that estrogens are equally effective sublingually as by intramuscular administration, while desoxyeorticoesterone, androgens, and pregneninolone require about 4 times larger doses.

2. Experiments on Rhesus monkeys with progesterone in propylene glycol-alcohol solution administered sublingually produced variable results, but suggest that 4 or 5 times the intramuscular dose is the effective minimum required.

3. Experiments on rabbits with progesterone in propylene glycol-alcohol solution produced extremely variable results which, however, suggest that the ratio of sublingual administration to subcutaneous is, as with the Rhesus monkey, at least 4 to 1.

4. Because of the variability of response and the larger dose requirement, sublingual administration of progesterone to monkeys and rabbits is evidently an unreliable method of administration.

I wish to thank Dr. Edward Henderson of the Schering Corporation, Bloomfield, New Jersey, for providing the progesterone in propylene glycol solution used in these experiments, and Dr. George W. Corner, Sr., for invaluable assistance and advice in carrying out this research.

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## EXPERIENCE WITH THE SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION (WATERS OPERATION)\*

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THE extraperitoneal cesarean operation has a very definite place in obstetric practice, particularly in cases where vaginal delivery has been attempted unsuccessfully or where there is evidence of intra-uterine infection. Sufficient experience with transperitoneal section plus sulfanilamide left in the peritoneal cavity is not yet at hand to indicate whether this latter procedure will or will not eventually replace the extraperitoneal procedure.

Our group of cases represents an attempt by a fairly large group of obstetricians and gynecologists to acquaint themselves thoroughly with the technique of the supravescical extraperitoneal section as described by Waters. Some of our cases would undoubtedly have been sectioned earlier, if we did not have this procedure at our disposal; on the other hand, there were a good many cases that were given a longer test of labor than usual, and thereby delivered vaginally.

In 1939 at a meeting of this society, E. G. Waters<sup>1</sup> reported a series of extraperitoneal operations using a technique whereby the lower uterine segment behind the bladder was approached by sharp dissection of the bladder fascia rather than by blunt dissection and in which he accomplished complete separation of the peritoneal fold from its attachment to the bladder—following the principle of Physick completely. It was this report that initiated our interest and is responsible for our present report. In 1940 J. V. Ricci<sup>2</sup> described a somewhat similar technique using a coiled-up catheter in the bladder to demarcate that organ instead of distending it with fluid.

The principle of the operation consists in separating the bladder from the attached peritoneal fold and thereby approaching the retrovesical lower uterine segment. This is made possible by the fact that each of the pelvic organs is covered by several layers of endopelvic fascia; by working between these layers the organs may be separated without injury. The fascial layers over the bladder seem to be multiple but are not distinct separate layers. The transversalis fascia continues down from above and over the bladder and behind the symphysis. Over the bladder it is intimately connected with the prevesical

\*Read at a meeting of the Brooklyn Gynecological Society, November 5, 1943.

fascia. The peritoneum reflected over the bladder is firmly adherent to the bladder while the vesico-uterine fold is loosely adherent to the uterus (and thus is easily reflected off the uterus, as in hysterectomy and low flap cesarean section). The point of reflection rises with advancement of labor.

### Authors' Modified Technique

The bladder is filled with 150 to 200 c.c. of methylene blue solution; the catheter remains in situ and connected with the container, so that the bladder may be emptied or refilled as desired.

The incision is about four inches long, starting about two inches below the umbilicus and extending to the symphysis; the incision is midline (or left paramedian) and through skin and superficial fascia. The skin is reflected to the left slightly, so that the fascia (anterior rectus sheath) is incised slightly to the left of the midline (in order to avoid injury to the peritoneum when extending the incision upward, and injury to the bladder when extending the incision downward); this incision in the anterior rectus sheath is extended downward to the symphysis, and upward over the rectus muscle to the upper end of the incision. If necessary the pyramidalis muscle is cut. The midline is approached, and the two recti muscles separated, exposing the distended bladder covered with transversalis fascia, and the peritoneal pouch coming down over the bladder dome. The transversalis fascia and the prevesical fascia are incised longitudinally (for about  $1\frac{1}{2}$  inches) below the peritoneal reflection; bluntly (with back of knife) these layers are separated laterally and superiorly from the bladder wall and these fascial layers are cut with scissors horizontally (making a T incision). Approaching the left vesico-uterine space inside the bladder fascial covering, the bladder is emptied of most of its contents and the fascia lateral to the bladder is incised longitudinally until the lower uterine segment is reached. A finger is then insinuated behind this fascia medially so as to separate the bladder and its posterior fascial covering from the uterus. The peritoneal fold is now put under tension so that its line of demarcation from the bladder stands out and this line is now incised sharply and carefully thus separating the peritoneum from the bladder. If the peritoneal cavity is accidentally opened, the opening is tied with a plain ligature rather than a suture. This dissection is carried across the top of the bladder from left to right. The bladder is now completely emptied and the fascia over the uterus below the vesico-uterine reflection of peritoneum (which now stands out clearly) is incised horizontally and the peritoneal fold pushed up over the uterus to a point high enough to give ample room for the extraction of the fetus. The uterus is incised in a horizontally crescentic incision (convex downward) and the fetus extracted using the hand as a vectis aided by pressure from above; this is done slowly to avoid extension of the uterine incision. Ergotrate is given intravenously at this point. The placenta is removed and the uterine wound sutured with two layers (second layer, Lembert) of continuous chromic suture avoiding the peritoneal fold superiorly. The bladder is again filled with fluid to make certain that there are no perforations or weak points. Bleeding on the bladder wall is controlled. The peritoneal fold is examined for injury. A Penrose drain is left behind the bladder; the fascia and skin are closed as usual.

### Report of Cases

From April, 1939, through early October, 1943, 100 cases of Waters' extraperitoneal section were done. We have divided these into 2 groups, indicated extraperitoneal sections and nonindicated extraperitoneal sections.

Arbitrarily we have chosen the following criteria for the indicated group: the presence of a temperature over 100° F. by mouth, membranes ruptured over 15 hours, or pains for over 24 hours. Our nonindicated cases would ordinarily have had a low flap section. There were 76 cases in the indicated group and 24 in the nonindicated.

In the first group 11 patients had temperatures ranging from 100 to 105° F., 53 cases had ruptured membranes for an average of 43.9 hours; and 61 cases had pains for an average of 48.7 hours. One case in this group of 76 had had an attempted forceps that failed.

There were 93 primiparas and 7 multiparas.

Indications for section for the entire series of 100 cases were: disproportion 44, primary uterine inertia 20, toxemia 8, elderly primipara 7, previous stillbirths 4, cervical dystocia 4, fetal distress 6, dystocia dystrophy syndrome 3, sterility 2, previous section 2. Most of these cases had several factors responsible for doing the section, but the most pertinent one was used for classification.

*Anesthesia.*—Spinal was used in 67 cases, gas-oxygen-ether in 27 and cyclopropane in 6.

There were 25 different operators in this group. The average operating time was 73 minutes with a range from 35 minutes to 135 minutes. As more experience was obtained, the operating time for each of the operators was considerably reduced.

The average blood loss was estimated to be 350 to 400 c.c. Two cases had an estimated loss of 700 to 800 c.c. and 2 others 1,000 c.c. each. Four patients were given transfusions.

*Peritoneal and Bladder Injuries.*—Of the 100 cases reported, 36 had one or more openings in the peritoneum. These were usually tied off with a ligature before the uterus was incised. Six of the 36 cases were found to have openings in the peritoneum at the completion of the operation. These 6 cases occurred in the earlier days of our experience and we learned that they were usually due to ligatures on the peritoneum placed under tension or insecurely tied. Openings in the peritoneum, as Waters has indicated, are best treated by ligature rather than suture ligature to avoid microscopic leak in the peritoneal fold through which bacterial invasion might theoretically take place.

Seventeen bladders were injured; fifteen had perforations that ranged in size from very small to quite large; one bladder was markedly thinned out in one area so that the mucosa was exposed; and one case where no injury was observed at the table developed a vesico-abdominal and vesico-vaginal fistula. This last case had profuse bleeding from large veins on the posterior bladder wall close to the lower segment and deeply placed suture ligatures undoubtedly produced sloughing of the bladder wall. All patients made uneventful recoveries. All bladder openings and areas of markedly thinned out bladder wall should be carefully repaired in layers and a retention catheter left in for at least 10 days. Three of our cases had vesico-abdominal fistulas. Two of these are mentioned above and a third one occurred in a case which

had a bladder perforation and was treated improperly: the catheter being removed on the fourth day. It was subsequently replaced for 10 to 12 days and healing occurred. All the fistulas eventually healed with the use of an indwelling catheter.

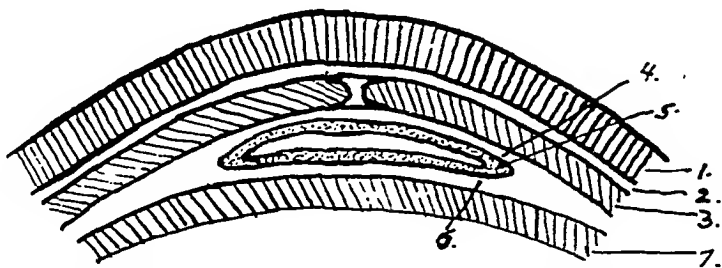


Fig. 1.—Schematic representation of anatomy, showing horizontal section below peritoneal reflection. 1. Skin and superficial fascia. 2. Anterior rectus sheath. 3. Recti muscles. 4. Fascia transversalis. 5. Bladder wall. 6. Posterior vesical fascia. 7. Anterior uterine wall. S. Peritoneum. 9. Symphysis.

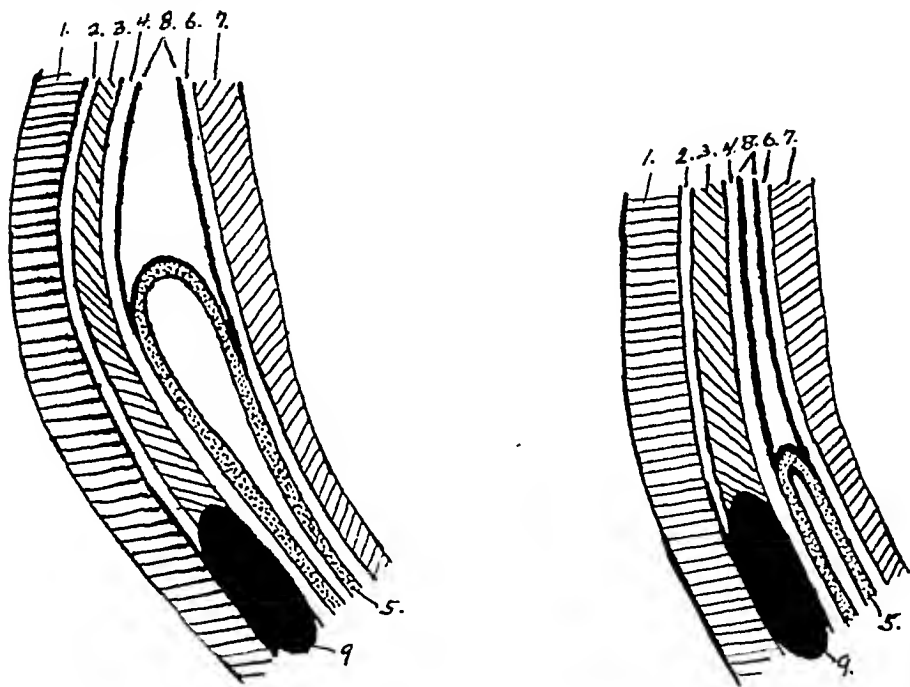


Fig. 2.—Longitudinal section, showing bladder distended and full.

**Morbidity and Mortality.**—There was no maternal mortality. Morbidity, exclusive of the first 2 postoperative days, occurred in 66 out of 100 cases. Fever ranged from 3 to 18 days with an average of  $5\frac{1}{2}$  days. Causes for morbidity were: wound infections, endometritis, parametritis, pelvic thrombophlebitis (one case). The average hospital stay was 15 days; the shortest was 10 days, the longest was 92 days (case of pelvic thrombophlebitis). Many of the cases drained from the lower angle of the drain site for 2 to 4 weeks. Ten had definite wound infections.

Two infants were stillborn and 98 lived. One stillbirth occurred in a case of severe amnionitis and the presence of a fetal heart was ques-

tionable at the time of operation. The other one was in one of the cases of fetal distress and the presence of a fetal heart was reported just before the incision was made.

### Discussion

Our experience with this operation is proof that a fairly large group can learn to do an extraperitoneal section successfully. Success depends upon an intelligent understanding of the anatomy of the pelvic fascia and its not infrequent variations. Many of the early failures with the extraperitoneal operation were due to a lack of clear understanding of the pelvic fascia, together with fear of bladder injuries. Throughout the history of extraperitoneal section there seems to have been an oft repeated pattern: first a small group of enthusiasts do the operation in a certain way; then other groups with very little experience and very little knowledge of the local anatomy involved, try to emulate the first group; they get into difficulties, and before long the operation is abandoned. In our own experience, the members of the group were able to do the procedure in shorter time and with less frequent peritoneal and bladder injuries as their experience increased and as their knowledge of the anatomy involved increased with it.

Our understanding of the anatomy of the pelvic fascia is such that we believe the bladder to lie or rest between several fascial planes or sheets rather than its being enclosed in a complete fascial envelope as has been described in most of the articles and texts. It is for this reason that the bladder cannot be completely dissected in a single plane out of its so-called fascial capsule from front to back, either superiorly or laterally. (See Figs. 1 and 2.) It is therefore necessary to incise the bladder fascia both anteriorly and posteriorly in order to reach the posterior bladder wall without injury. This dissection can be done either bluntly or with the knife, although we favor sharp dissection.

There are a number of points in the technique that we have found particularly helpful. First, the bladder should *not* be overdistended with fluid: a very thinned-out bladder wall due to overdistention, is difficult to dissect and easily perforated. Secondly, the lateral approach to the posterior vesical fascia should be made with the bladder empty and as low down as possible in order to avoid injury to a low dipping utero-vesical peritoneal fold. Thirdly, in the lateral dissection, the remaining anterior vesical fascia and the posterior vesical fascia are incised sharply until the glistening surface of the lower uterine segment comes into view. It is only by doing this that we can be certain to get posterior to the bladder and its posterior fascia without injuring the bladder wall, because the dissection will then take place between two definite fascial planes, instead of between bladder wall and posterior bladder fascia. Fourth, the peritoneum is dissected off the bladder dome by sharp dissection, hugging the bladder wall

rather than the peritoneum. Fifth, the pelvic fascia on the anterior lower uterine segment is incised transversely, thus mobilizing the uterovesical peritoneal fold which can then be pushed off the lower segment as far as desirable, giving us plenty of room for the incision. Sixth, the incision should be fairly large to avoid difficulty in extracting the baby and also to avoid extension in the uterine wall. Seventh, the head is most easily delivered with the hand after all retractors have been removed from the operative field. Eighth, all bladder injuries, small or large, must be repaired in 2 or more layers. Defects or thinned-out areas in the bladder wall should also be repaired in layers. All repaired bladders should have a retention catheter for at least 10 days. Ninth, the dissection of the bladder fascia can be carried out successfully even when the patient is not in labor, although it is usually easier with advanced labor. In this connection, we did the dissection successfully in a patient 27 weeks pregnant, not in labor, but found that extraction of the fetus was difficult due to the absence of a well-formed lower segment giving a very limited space for the uterine incision. Tenth, care should be exercised in retracting the peritoneal flap after its dissection from the bladder dome whether this be done by hand or with retractors. The retractor edges should not be sharp to avoid peritoneal injury.

Theoretically, the number of cesarean sections done on a large obstetric service, should definitely decrease, as borderline disproportion cases can be given a much more thorough test of labor. Similarly, cesarean section mortality should decrease because the danger of peritonitis is almost entirely eliminated. In our hospital, during the same period of four and a half years during which the 100 cases herein described were done, there were 444 other cesarean sections, with 4 deaths (one embolic, one anesthetic and two peritonitis deaths)—giving an overall cesarean section mortality rate of less than 0.74 per cent: this is much less than any other similar series of 544 cases at our hospital and also much less than our previously reported cesarean section death rate. We feel quite strongly that this marked reduction in our cesarean section mortality is in a large measure due to the extraperitoneal procedure.

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### Discussion

DR. EDWARD G. WATERS.—The subject of sulfanilamide in actually and potentially infected transperitoneal operations is of great importance. Few of us who have had extended experience with sulfa drug therapy have any doubts as to its value and efficacy in handling infected patients. There can be no doubt about its value when used intraperitoneally. But since many patients with peritonitis who have had sulfanilamide used intraperitoneally still die of peritonitis, we do

not think that a transperitoneal operation with such semispecific therapy as is now available can compare with an extraperitoneal operation.

Since a forceps blade is smaller and more easily manipulated in the lower uterine segment than is a hand, we routinely use a forceps blade applying it in a lifting and prying manner like a vectis. We do not hesitate to do a version if there is difficulty with the head.

The lower uterine segment differs in character not only in patients who have been in labor but also in patients who have not been in labor. In general, the lower segment tends to thin out as labor progresses but we have seen some very thick segments in women who have had prolonged labors and we have seen extremely thin segments in women who have had no labor whatsoever. The character of the physiologic prelabor contractions of the uterus, especially in the last two months of pregnancy, exerts a marked effect on the lower uterine segment.

The cesarean incidence in my practice has dropped from nearly 4 per cent to 2.4 per cent in the last several years since we have more widely used extraperitoneal sections. We have delivered many patients vaginally, who previously would have had cesarean sections, by giving them an adequate test of labor with the possibility of an extraperitoneal section held in reserve.

The mortality of all our sections was 1.18 per cent. In the last eleven years we have had 21 section deaths in 1,771 cases. In the lower segment operations, there were 12 deaths or 1.06 per cent. In the extraperitoneal operations, there were 3 deaths or 0.83 per cent. In the 163 cases done by the Latzko technique, we had 2 deaths or 1.2 per cent. In over 208 cases done by the technique described here this evening there was one death, a mortality rate of 0.48 per cent. Thus there is actually a lowered mortality in potentially and actually infected cases, where by all reasoning one might expect it to be much higher. There can be no disputing the safety of an operation where a recognizedly worse risk still has a much better chance than the clean risk patient.

DR. MERVYN V. ARMSTRONG.—I would like to ask Dr. Waters if he can tell us how his cases could be divided into the necessary and the purely elective variety. I am interested to know the cause of the death in his one fatal case.

DR. WILLIAM F. NELMS.—I would like to inquire of Dr. Waters whether he has had occasion to do this operation a second time on the same patient and if so, whether he found great difficulty in exposing the lower uterine segment because of adhesions.

DR. EDWARD G. WATERS.—I have operated upon ten patients who had previous extraperitoneal sections. Obviously, an obstetric risk sufficiently bad to require an extraperitoneal operation the first time should not be left long in a subsequent labor. In the majority of the patients it was possible to operate extraperitoneally a second time, but in two patients it was not possible to do so. These patients had extensive cellulitis, marked scar formation, and the tissue was too adherent to separate. Both were converted into transperitoneal exclusion operations.

I cannot tell offhand how many of those 235 cases were necessary and how many were purely elective. On my own private cases I think possibly eight out of ten cesarean sections are extraperitoneal operations, just to demonstrate the technique. These patients make a satisfactory recovery after operation for they have had no peritoneal handling and no shock is induced. None die from pelvic cellulitis, when drained.

DR. ISIDORE DAICHMAN.—Dr. Waters brings up the question of extraperitoneal section with sulfanilamide versus transperitoneal section with sulfanilamide. At the present time there can be no question that the former procedure

is preferable, and is in fact the procedure that we frequently follow. However, we must be open minded about the possible eventual efficiency of chemotherapy. It is not at all impossible that chemotherapy may eventually completely replace the need for the extraperitoneal procedure.

From our experience with the supravescical extraperitoneal procedure, we feel that while each organ has its own intrinsic fascia, it also rests or "slides" between distinct fascial planes or sheets of the transversalis fascia, which, in the pelvis, splits to allow each of the organs to rest between clearly defined fascial layers. It is by working between these layers that the dissection can be accomplished without injury to the organs.

There is no question that clinically these patients run a much smoother post-operative course than they do after a transperitoneal approach. Abdominal distention occurs infrequently, and when it does occur, it can be faced with the assurance that we are not dealing with a peritonitis since the peritoneal cavity has not been invaded.

One cannot fail to be impressed by the marked reduction in our cesarean section mortality during the period of time covered by this report. Dr. Waters' figures are likewise impressive. There can be no doubt that a large measure of this is due to the use of the extraperitoneal procedure in those cases that would normally carry the highest operative risk. Furthermore, our experience indicates that the technique can be successfully mastered by any group of competent obstetric operators; that the complications are not formidable enough to prevent a group from overcoming them. Moreover, the operating time and incidence of complications will diminish considerably as experience with the operation increases.



## PAIN THRESHOLD IN DYSMENORRHEA

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WHILE many interesting theories have been advanced as to the mechanism giving rise to dysmenorrhea, no study has been made of the difference in pain threshold between dysmenorrheics and nondysmenorrheics.

The question arises as to whether dysmenorrheic patients actually receive more intense pain stimuli than do nondysmenorrheics, or whether they are merely more sensitive to pain than their more fortunate sisters. It would also be worth while to determine whether or not the two groups of women differ in sensitivity to pain after they have reached the menopause. Furthermore, how do males react to pain in comparison with normal, dysmenorrheic and postmenopausal females?

A lowering of the pain threshold in dysmenorrheics, as compared to normal women, has been suggested by many authors, but up to the present, experimental evidence to substantiate this hypothesis has been lacking. Studies on pain threshold have, however, been carried out on normal persons, as well as on psychoneurotic, hypothyroid, hypo- and hypersensitive individuals. In normal men and women, pain sensitivity, as measured by reaction to thermal stimulation, has been found to be relatively stable and uniform, both in the same subject<sup>1</sup> and in different subjects.<sup>2</sup> It also appears to be independent of age, sex, lack of sleep, or emotional factors.<sup>2</sup> More recently, however, considerable variation in pain threshold has been reported in a group of college women tested by an electric method.<sup>3</sup> No explanation for the variability was offered.

Both thermal and electric methods, as employed by these investigators and by others,<sup>4</sup> were considered impractical for the present study, since these procedures require too much time and equipment. A simple mechanical test had been devised by Libman<sup>5</sup> who measured pain threshold by pressing firmly against the styloid process of the mastoid bone. The disadvantage of this method, however, was that the amount of pressure had to be gauged by the investigator; the results, purely qualitative, were therefore subject to considerable error because of the personal factor involved. Hollander<sup>6</sup> also induced pain by mechanical means, using a grater attached to a blood pressure cuff; this method was employed in a small series of experiments by the present author, but was discarded because of the cumbersomeness of the apparatus. It is interesting that the figures obtained by Hollander's technique agree with those of the larger series reported in the present paper in which pain was also induced by pressure, with the sensimeter.

### Procedure and Material

The sensimeter was employed in the present study because it gives accurate objective results and can be used conveniently anywhere with a minimum expenditure of time. This instrument has been adapted by Pehner<sup>7</sup> from the Geneva Lens Measure by moving the fixed points 7 mm. apart. The salient feature of the sensimeter is a central movable point which is attached to a hand on a watch dial. The tests were made on the proximal phalanx of the thumb which was held horizontally while the distal phalanx was held at right angles to it. The

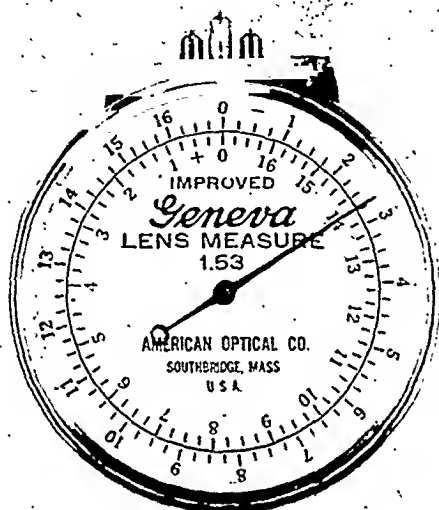


Fig. 1.—Sensimeter.

sensimeter was rested upon the proximal phalanx, and the dial number noted which registered the weight of the instrument. Pressure was then applied until the subject drew away or winced; at this instant the corresponding number on the dial was read. The figure registered on the dial before the pressure was exerted was subtracted from the second reading, and the difference was recorded. This procedure was then repeated on the other thumb. The mean of the two values represents the subject's pain sensitivity.

In this study the average pain threshold of 100 dysmenorrheic women was compared with that of 100 nondysmenorrheics, 100 women past the menopause,\* and 100 male subjects. The dysmenorrheic group consisted of 50 individuals with so-called *primary* (essential, "intrinsic") dysmenorrhea, and 50 with *secondary* (acquired, "extrinsic") dysmenorrhea. One-half of the postmenopausal group was composed of women who had gone through the physiologic change of life, and the remaining half consisted of those in whom the menopause had

\*In the postmenopausal group, the time interval since the last menstrual period ranged from two months to twenty-five years.

resulted from surgery. Furthermore, each of these two subgroups was equally divided into women who had had dysmenorrhea and those who had been free of pain with the menses.

### Results

Table I shows the dysmenorrheic group to have a lower pain threshold than any of the other three groups tested; i.e., 12.2 for the dysmenorrheics, as compared to 14.9 for nondysmenorrheics; 15.2 for postmenopausal women; and 14.6 for males. The average of all three groups of women was 14.1, and the average of all four groups of subjects studied was 14.2. Thus the dysmenorrheic group average was 2.7 units below that of the nondysmenorrheic group, 1.9 units less than the average of the three groups of women, and 2.0 units less than the average of all four groups of subjects tested.

TABLE I. PAIN THRESHOLD IN FOUR GROUPS OF HUMAN SUBJECTS AS MEASURED BY THE SENSIMETER

GROUP	NO. OF CASES	AVERAGE PAIN THRESHOLD MEAN OF READINGS FROM RIGHT AND LEFT THUMB (SENSIMETER UNITS)
I. Dysmenorrheic	100	12.2
(a) Primary	50	11.4
(b) Secondary	50	12.9
II. Nondysmenorrheic	100	14.9
III. Postmenopausal	100	15.2
(a) Surgical	50	15.2
1. Had dysmenorrhea	25	14.7
2. Had no dysmenorrhea	25	15.6
(b) Physiologic	50	15.3
1. Had dysmenorrhea	25	14.4
2. Had no dysmenorrhea	25	16.2
IV. Male	100	14.6
All women	300	14.1
All subjects	400	14.2

Patients suffering from the primary type of dysmenorrhea showed the highest sensitivity of any group or subgroup in the entire series studied: a threshold of 11.4, as compared to 12.9, obtained in the group of those afflicted with the secondary type of dysmenorrhea.

The highest threshold, i.e., the lowest sensitivity, of all four groups, on the other hand, was recorded among the postmenopausal women, 15.2. No explanation is offered for this finding. The average pain threshold of the surgical menopausal subjects was only 0.1 unit less than that of women who had gone through the natural menopause, 15.2 and 15.3, respectively. However, it is of interest to note that individuals who had had dysmenorrhea earlier in life showed a decidedly lower threshold than those who had experienced no pain with their periods. This is true of both major groups of menopausal subjects, e.g., 14.7 (surgical menopause), and 14.4 (physiologic meno-

pause), in those with a history of dysmenorrhea, as against 15.6 (surgical menopause), and 16.2 (physiologic menopause), in women who had been free of pain at catamenia.

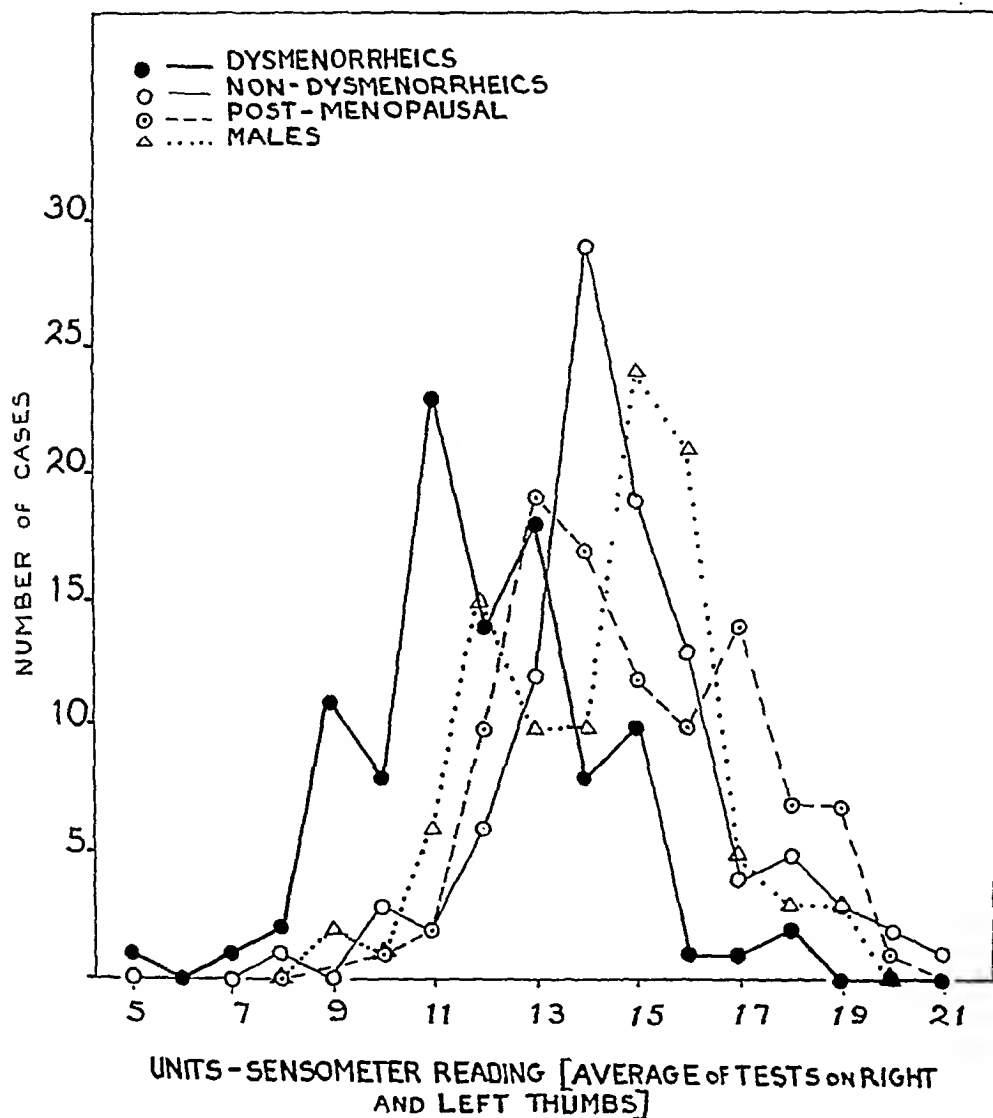


Fig. 2.—Curves showing the preponderance of dysmenorrheics in the low threshold area and their relative infrequency in the high threshold areas as compared to other individuals.

The pain threshold of the male subjects was 14.6, only very slightly higher than that of the average of the three groups of women (14.1). Likewise, the reaction to pain of men did not differ significantly from that of normal and postmenopausal women (14.9 and 15.2, respectively). Thus, if one excludes the dysmenorrheics, the group in which sensitivity to pain was markedly greater than in the other groups of women studied, it appears that in normal subjects pain threshold is in general independent of sex, an observation previously reported by Schumacher and his co-workers.<sup>2</sup>

Since deductions based on average figures alone may often lead to erroneous conclusions, frequency distribution curves were plotted for the four groups of subjects tested (Fig. 2). These show the variations within each group. While a mathematical analysis of the results has not been attempted, comparison of the modal values in the four groups confirms the conclusion derived from average figures as to the relatively high degree of pain sensitivity of dysmenorrheics.

It should be pointed out that in comparing the reactions of normal and of dysmenorrheic women to pressure stimuli on the thumb, as in the present investigation, the question might be raised as to the validity of making inferences from a study of pain elicited on the surface of the body to pain that would be experienced by dysmenorrheic women at the time of menstruation. However, recent experimental evidence indicates that a parallelism between superficial and deep pain does exist, and that "inferences drawn from the studies of superficial pain are valid for deep pain."<sup>8</sup>

### Summary and Conclusions

1. The hypothesis, often suggested, that dysmenorrheics have a lower pain threshold than normal women, has been substantiated by a study of 400 subjects, comprising 100 dysmenorrheics, 100 nondysmenorrheics, 100 women past the menopause, and 100 males.

2. The average pain threshold of the dysmenorrheic group was lower than that of any of the other three groups of subjects tested. Women suffering from the primary type of dysmenorrhea showed a higher sensitivity than those afflicted with the secondary type. When frequency distribution curves were plotted for the four groups of subjects studied, a comparison of the modal values confirmed the conclusion derived from average figures as to the relatively high degree of pain sensitivity of dysmenorrheics.

3. The highest average pain threshold of any group was noted in women past the menopause. Those who had a history of dysmenorrhea showed a lower threshold than those who had had painless periods.

4. If one excludes the group of highly sensitive women, the dysmenorrheics, pain threshold does not appear to be markedly affected by sex.

5. Since a study of pain sensitivity within the postmenopausal group indicates that the lowered pain threshold of the dysmenorrheic is retained even past the climacteric, there apparently exists in the constitution of the dysmenorrheic woman an intrinsic factor that renders her more susceptible to pain than the nondysmenorrheic individual.

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490 POST STREET

## DIMETHYL-ETHER STILBESTROL IN THE MENOPAUSE AND FOR THE SUPPRESSION OF LACTATION

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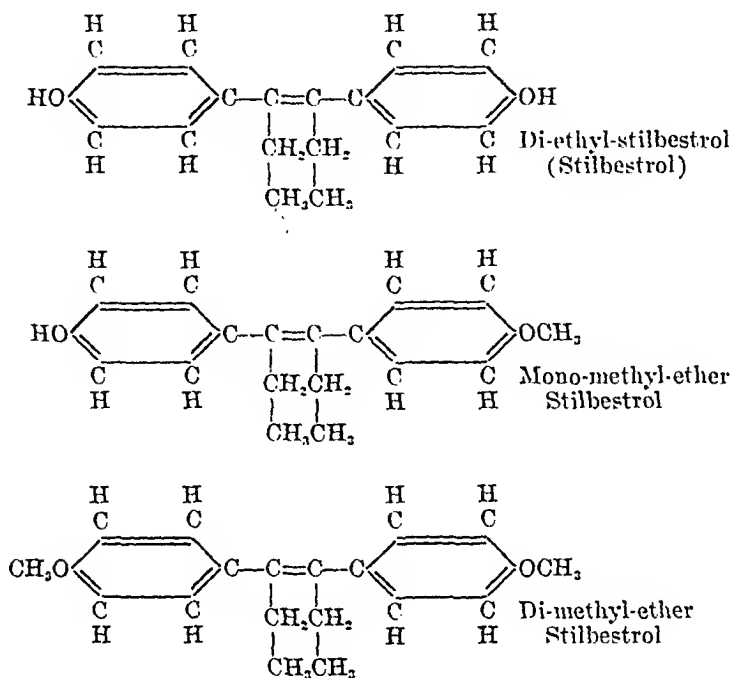
**D**IETHYLSTILBESTROL, usually referred to as stilbestrol, has not proved wholly satisfactory in the therapy of either the menopause or in the suppression of lactation. In the former, toxic reactions ranging from 10 per cent to 50 per cent according to various authors, and varying from simple nausea and vomiting to exfoliative dermatitis and angioneurotic edema, are the chief objections. In the suppression of lactation, the author found stilbestrol adequate during the parturient's stay in the hospital. However, reports from patients two weeks' post partum revealed a large percentage with reingorgement of the breasts. Further added treatment with stilbestrol, in these cases, resulted in an alarmingly profuse first menstrual period. This added data necessitates revision of the value of the results obtained and reported previously by this author.

During the last two years, numerous articles have been published dealing with a host of new synthetic estromimetic agents, the majority of them derivatives of stilbestrol. These are the fatty acid salts (dipalmitate, dipropionate and benzoate), dihydrostilbestrol (hexestrol), and the methyl ethers. The greater number of these reports are comparison studies of dosage, therapeutic efficacy, and toxicity between stilbestrol and several of its salts. Although some of these compounds are less toxic than stilbestrol, it must be emphasized that none of these are entirely free from "unpleasant sequelae." It is an accepted fact at present that by increasing the length of the side chain of stilbestrol, or by stearification with the aliphatic acids, there is a decrease in potency and toxicity, for the same dosage level, but a more prolonged estrus effect. However, the ideal synthetic estromimetic, that is, potent and free from all toxicity, has not as yet been described.

The case for the methyl ethers is aptly summarized by Teague, as follows: "A few papers have appeared recently concerning monomethyl stilbestrol. This ether derivative presumably becomes demethylated in the body, liberating free diethylstilbestrol. It seems to offer the advantage over free diethylstilbestrol of producing fewer side-actions in the effective dose range."

The above paragraph stimulated further investigation in the chemistry and pharmacology of the methyl ethers of stilbestrol. Notwithstanding the excellent reported results with monomethyl ether stilbestrol, the author felt that the dimethyl ether stilbestrol, because of

its chemical configuration, might be still more efficacious. The following structural formulas, of stilbestrol and its mono- and dimethyl ether derivatives, show the differences between the three chemicals, i.e., the substitution of one methyl radical for each hydroxyl group, making either a mono- or a dimethyl ether out of the original diphenol.



In the laboratory, great difficulty is experienced in the demethylation of the methyl ethers, by chemical means. Furthermore, it is believed that since methyl radicals are ethers, they would also be more stable to oxidation in the organism, resulting in more prolonged and uniform activity, depending upon the rate of demethylation and utilization. However, there is no authoritative statement on the relative rapidity of absorption and oxidation, of the methyl and ethyl radicals, permitting prognostication as to clinical results of therapy with these agents. Nevertheless, the difficult chemical demethylation, in vitro as well as in the organism, offers a reasonable pharmacologic explanation of the clinical results herewith obtained and reported.

### Menopause

This group of cases studied represents 22 from the gynecologic clinic of Dr. M. N. Hyams at the N. Y. Post-Graduate Hospital and 27 from the author's private practice, treated and observed for the past 18 months. This mixed group of women from all social strata makes possible the elimination of psychic factors in improvement, prevalent in the therapy of the menopause, particularly in private patients. Every patient originally applied for relief from "change of life." All complained of flushes, sufficiently frequent during the day to interfere



with the usual routine and severe enough to arouse them from sleep. One patient suffered from flushes occurring every ten minutes and threatened suicide unless relieved. Associated with the vasomotor symptoms of flushes, chills, and sweats were symptoms referable to the nervous system, such as melancholia and irritability, in some cases.

The sole method of assay used was the patient's reactions, as advocated by Greenhill. Liberation from symptoms meant successful therapy and absence of side-actions indicated freedom of toxicity from the drug.

*Method.*—Dimethyl ether stilbestrol, 30 mg. dissolved in 1 c.c. of sesame oil, was injected intramuscularly and repeated weekly until all symptoms subsided. One patient received 60 mg., 3 were given 75 mg., and one required 120 mg. With the exception of these five, the other 44 cases received 90 mg. We can therefore assume the average dose necessary for complete relief to be 90 mg. divided into three weekly doses of 30 mg. The patient was then instructed to return at monthly intervals for observation. No supplementary oral treatment of any kind was given. When the symptoms recurred, a similar course of treatment was instituted. The total number of symptomless days was computed and served as the index of the efficacy of the drug, in each individual case.

*Results.*—The results obtained with dimethyl ether stilbestrol more than fulfilled all expectations, as to potency, duration of effects, and absence of toxicity. Table I is a résumé of these findings.

TABLE I

TYPE OF MENOPAUSE	CLINIC CASES	AVERAGE NUMBER DAYS SYMPTOM-FREE	PRIVATE CASES	AVERAGE NUMBER DAYS SYMPTOM-FREE
Natural	17	144	18	156
Surgical	5	112	9	121
Total	22	132	27	144
Toxic Reactions	0		0	

It will be noted that the average number of days, free from any symptoms referable to the menopausal state, are 132 for clinic cases and 144 for the private, with a mean average of 138 days for the entire group. Noteworthy is the inexplicable shorter duration of relief in the surgical menopause cases as compared to those in the natural menopause, i.e., 112 against 144 days in the clinic group and 121 against 156, in private cases. The author is unable to find any record of this observation, in the literature, and will appreciate correspondence, either confirming or denying the constancy of this finding. The one most significant fact is the total absence of any toxic reactions. Careful questioning failed to elicit an admission of even simple nausea. The prolonged potent effects and freedom from any toxic side-actions stamp dimethyl ether stilbesterol as the possible ideal estromimetic.

### Suppression of Lactation

This part of the study was carried out at the Menorah Maternity Division of the Beth-El Hospital, Brooklyn, with the cooperation of the obstetric staff.

It is apparent, because of its long period of latent activity, that dimethyl ether stilbestrol, per se, could not be of any value in suppression of lactation. However, in combination with stilbestrol a mixture is obtained in which both drugs are supplemental, in much the same way as obstetric pituitrin and ergotrate. The stilbestrol, a quickly-acting suppressant, makes possible the symptom-free period until the slower acting dimethyl ether stilbestrol exerts its prolonged effects, thereby diminishing the secondary reingorgement, so frequent with stilbestrol alone. In this study, 15 mg. of stilbestrol and dimethyl ether stilbestrol, dissolved in 1 c.c. of sesame oil, were administered intramuscularly and repeated in 48 hours.

A total of 269 cases were treated and observed in the manner outlined. Of these, 245 received but the two injections and 24 required a third one, administered usually on the day of discharge from the hospital. Four cases were complete failures, judged by painful and engorged breasts, requiring some other form of relief. These patients may have been refractory to these estrogens. Obviously, the problem of reingorgement is of paramount importance in a study such as this, and every effort was made to ascertain the total number of cases, reporting any degree of reingorgement. Included in this group are cases that required no further therapy or relief. Yet their inclusion was thought advisable, to rule out all element of doubt as to the therapeutic efficacy of this mixture. Approximately 11 per cent suffered with reingorgement. This is probably due to improper supervision. The author believes that a third dose of the mixture would have prevented this complication, for in the 24 cases receiving three injections there was no incidence of reingorgement.

TABLE II

NUMBER	CASES	WITH RE-INGORGE- MENT	TOTAL FAILURES	DOSAGE
With 2 doses	245	29	0	30 mg. stilbestrol 30 mg. dimethyl ether stilbestrol
With 3 doses	24	0	4	45 mg. stilbestrol 45 mg. dimethyl ether stilbestrol
Total	269	29	4	

Delay in onset of menstruation occurred in about 30 per cent of the cases—in some for as long as two months past the usually expected time. This fact serves not only to explain the mechanism of suppression of lactation, by inhibiting the anterior pituitary gland in its production of prolactin, but is a direct indication of the pharmacologic activity of the estrogens employed. One case of profuse bleeding, four weeks post partum, necessitated a curettage, which revealed a cystic glandular hyperplasia of the endometrium.

As a whole, these results may be regarded as satisfactory. However, it is not the intention to allow the formula of the mixture and the

dosage to remain static. This investigator is not aware of any similar or previous study, with a mixture of estrogens, in the suppression of lactation, and hopes that this may serve as a stimulus to further studies. Improvement in results will undoubtedly be attained by continuous experimentation, for the optimum mixture and method of administration.

### Summary

1. In the menopause, dimethyl ether stilbestrol gives the following results:

- a. Absence of any toxic reactions,
- b. Freedom from symptoms referable to the menopause for an average period of 138 days or approximately four and one-half months, and
- c. Patients with surgical menopause have a shorter duration of relief than those in a natural menopause.

2. In the suppression of lactation, in a mixture with stilbestrol,

- a. The incidence of reingorgement was reduced,
- b. The onset of the first menstrual period was delayed, in 30 per cent of the cases.

The author wishes to express his appreciation to Dr. M. N. Hyams for his permission to utilize the clinic patients in this study; to Drs. Halperin, Levine, and Koplowitz for their generous cooperation and permission to treat their private and service obstetric cases, for the suppression of lactation, thus making this study possible.

The material used was supplied by W. F. Straub & Company, Chicago, Ill. The dimethylether stilbestrol is known under the name of Synthil A. The combination of estrogens used in the study of suppression of lactation was also prepared by the same company. The author wishes to thank this company for its cooperation and for the materials supplied.

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# PROLONGATION OF PREGNANCY AND EXCESSIVE FETAL DEVELOPMENT FOLLOWING ADMINISTRATION OF CORPUS LUTEUM EXTRACT IN THE TREATMENT OF THREATENED ABORTION

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SNYDER<sup>1</sup> administered extract of pregnancy urine to rabbits late in gestation. Fresh corpora lutea resulted, the onset of parturition was delayed, and the fetuses developed to excessive size.

Heckel and Allen<sup>2</sup> treated rabbits late in pregnancy with estrogenic substance. The fetuses died shortly after the maternal treatment, but nevertheless the onset of parturition also was delayed.

Koff and Davis<sup>3</sup> administered corpus luteum extract to rabbits late in pregnancy. This treatment delayed the onset of parturition, and the resulting fetuses showed evidence of postmaturity by their unusual size and state of development.

Snyder considered that the prolongation of the pregnancies of his animals was due to the activity of the experimentally produced corpora lutea. Heckel and Allen assumed that the same phenomena in their animals resulted from the fact that the estrogenic substance maintained the functional activity of existing corpora lutea. Koff and Davis concluded that the corpus luteum played a definite role in controlling the gestations of their rabbits.

The present report concerns a patient who received a large amount of corpus luteum extract during the first half of her pregnancy, which was administered in order to control a threatened abortion. Her pregnancy persisted for 44 weeks and her infant was unusually large at birth.

## Case Report

Mrs. A. S., white, aged 31, had had her first pregnancy terminate by a spontaneous abortion in July, 1942. Normal menstruation, which had always been regular, became re-established immediately. Her last normal period began January 3, 1943. Nausea was experienced for the first time on January 25. Uterine cramps began on February 6. Slight uterine bleeding occurred on February 21 and recurred several times between that date and March 21 when it appeared for the last time. Uterine cramps of variable strength and duration recurred frequently at irregular periods daily from their onset on February 6 until June 6, at which time they ceased. During practically this entire time the patient remained in bed.

For the 4 months while uterine cramps were taking place, the patient took orally an average of 14 grains of corpus luteum extract\* daily, consuming in this period some 1,500 grains of the material.

\*Corpus luteum was administered orally in the form of Lutein (Hynson, Wescott and Dunning Co.). According to the manufacturer, each 2-grain tablet represents approximately 8 grains of fresh corpus luteum of the sow, freed as far as practical from other ovarian tissue, and dried in a vacuum. The patient took an average of seven tablets daily, and more on days when cramps were unusually severe or frequent.

Fetal activity was experienced for the first time on May 16, during the twentieth week of gestation. On the basis of her menstrual history and other findings, the expected date of her confinement was computed as being October 10.

At the end of the second and third weeks after the expected date of confinement the patient took castor oil with the hope of starting labor, but this was without any effect upon her uterine motility. On November 6, which was 26 days after the expected date of confinement, labor began spontaneously. After 36 hours of uterine contractions of only fair strength the fetal head had failed to engage, and the cervix was dilated only 4 centimeters. As a result, the patient was delivered by cesarean section, the infant being found to weigh 4,990 grams (11 pounds).

### Comment

Certain questions arise in connection with this case. Was the pregnancy actually prolonged? In support of a positive answer to this question are the following facts: The mother of the infant was an intelligent college graduate. Her menstrual history was always regular. The date of her last menstrual period was known accurately and this period was normal. She experienced nausea within four weeks of her last period. Life was felt during the twentieth week of gestation. Castor oil failed to elicit a uterine reaction on two different occasions after the expected date of her confinement. The patient kept a daily record of all signs and symptoms until all evidence of threatened abortion ceased.

With respect to the size of the infant, the following facts are of interest: The mother weighed only 140 pounds before conception, and the father weighed 160 pounds, neither of them being of unusually large size. The infant was the first born; large infants usually are the later born in a family.

No information was available regarding the biologic potency of the corpus luteum extract. The patient, however, failed to abort in spite of the fact that cramps persisted for 4 months, and she did so previously at a time when she received no treatment with corpus luteum extract.

No similar experience has been unearthed in the literature, and this may have been due to the fact that probably no other patient received so large an amount of the drug over such a long period of her pregnancy.

If one assumes that this pregnancy was prolonged as a result of the administration of corpus luteum extract, its action remains to be explained. Two possibilities can be considered: Either the drug remained potent in the body, or its presence early in pregnancy spared the patient's own corpus luteum to be effective later in pregnancy. There may be no correlation between the treatment of this patient, and the length of her gestation and the large size of her child, but the above-mentioned experimental evidence would seem to be highly confirmative.

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# SPINAL ANESTHESIA TO FAVOR RAPID DILATATION OF THE CERVIX IN OBSTETRIC EMERGENCIES

## Preliminary Report

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OCCASIONS arise in obstetric practice where immediate delivery is imperative. These occasions fortunately are few, but nevertheless if poor results and tragedy are to be avoided, they must be treated by a technique that will be both effective and safe. Ordinarily when confronted by a case of prolapsed umbilical cord, irregular fetal heart, etc., our most important guide to treatment is the condition of the cervix. In the absence of disproportion, given a soft and dilatable cervix, the accoucheur usually completes the dilatation manually and then effects delivery by either forceps, internal podalic version or breech extraction depending on the presentation, position, degree of engagement and his own preference. Should a similar set of conditions present themselves in a case where the cervix is thick and leathery and not dilatable, the case is usually treated by attempts at cord replacement, at best a procedure that yields poor results, or by Dührssen's incisions of the cervix, or perhaps by cesarean section. In a great many cases the fetus is abandoned, the labor being conducted solely in the interest of the mother. Few obstetricians fortunately have the temerity to forcibly dilate the cervix and then effect delivery.

In the types of cases under discussion, I have employed spinal anesthesia with highly satisfactory results.

Delmas<sup>1</sup> in 1929 reported delivering women before the onset of labor by manually dilating the cervix and performing internal podalic version. Anesthesia was induced by the spinal route. This procedure at that time and even now impresses me as unnecessarily meddlesome and radical. However, given the proper indication this procedure can prove invaluable. Within the last few months, I have delivered a number of women by this technique, the results and conclusions of which will be reported in a subsequent paper by the author and Dr. Joseph Feibush who administered the anesthetics and worked out important details such as the preferred anesthetic agent, the optimum dosage, etc., and has also made careful and important observations of physical and mental reactions of patients during and following anesthesia.

The following cases illustrate both the indications and the technique employed.

My first delivery by this method was in 1939.

CASE 1.—Mrs. M. F., aged 27, gravida v. All the previous pregnancies ended in stillbirths in the seventh month of pregnancy. She was told that all of her pregnancies were complicated by toxemia. On the present admission to the hospital, the urine showed four plus albumin and the blood pressure was 132/82. Labor was induced medically three days after admission by castor oil and injections of Pitocin. The membranes ruptured that day but there were no labor pains. Leakage of amniotic fluid continued and at the end of two weeks there were still no appreciable labor pains. The cervix at this time was two fingers dilated and a Voorhees' bag was inserted. The bag was ineffective for despite its presence plus the administration of oxytocics, there were only irregular uterine contractions. Two days after the insertion of the bag, the patient had a chill and the temperature rose to over 103 degrees F. Her condition appeared desperate and immediate delivery was deemed imperative. The cervix at this time was three and one-half fingers dilated but thick. Inhalation anesthesia was considered inadvisable and delivery by the Delmas' technique was decided on.

Under spinal anesthesia, employing 1.3 c.c. tropococaine, the Voorhees' bag was removed. At the junction of the cervix and the lower uterine segment there was a marked contraction. This was dilated manually for some time, and when it disappeared podalic version was performed. The child showed several small areas of maceration and there was a loose knot in the umbilical cord. The placenta was expelled by the Credé maneuver. The entire procedure took thirty minutes. The relaxation was good, the respirations were regular and there was no vomiting. The patient had a stormy convalescence but left the hospital in good condition.

CASE 2.—Mrs. A. B., aged 36, gravida iii, para o. The last menstrual period was on September 23, and expected date of delivery June 30. I saw her with her family doctor on July 13, the reason for the consultation being an irregular fetal heart rate. The rate varied between 100 and 180 per minute. The fetus appeared to be average size and the pelvis ample. The cervical canal was obliterated and the cervix admitted the tip of a finger and was soft.

Under spinal anesthesia employing 150 mg. of procaine the cervix was easily dilated manually to full dilatation in seven minutes and a podalic version was performed. A normal living infant was easily delivered. The placenta was delivered a few minutes later by simple expression. Small bilateral cervical lacerations were repaired as was a right lateral episiotomy. Mother and baby left the hospital in ten days in good condition.

CASE 3.—Mrs. J. S., aged 28, gravida i, para o. Last menstrual period December 23, expected date of delivery September 30, 1943.

Patient went into labor on September 21, and after twelve hours of labor, the fetal heart became very irregular and violent fetal movements were observed. The fetus was evidently in distress and immediate delivery was deemed necessary.

Under 80 mg. of neocaine the cervix was found to be thick and one finger dilated. The position was right occipitoposterior and the head unengaged but engageable. Full cervical dilatation was easily obtained by manual dilatation. The occiput was then rotated to left occipito-anterior by a manual maneuver previously described by the author.<sup>2-3</sup> Axis traction forceps were then applied cephalically and a normal living

infant delivered. Moderate-sized cervical tears were easily repaired as was a right lateral episiotomy. The placenta was delivered by simple expression.

Mother and baby left the hospital on the ninth post-partum day in good condition.

CASE 4.—Mrs. B. F., aged 27, gravida ii, para i. Patient came from Arkansas and was very anxious to get back to her family. The menstrual history was indefinite, but judging from the size of her abdomen and the day she said she felt life, I deemed her at term on August 12, and proceeded to induce labor by rupturing the membranes. The cervical canal was obliterated and the cervical os was thick and admitted two fingers. The cord prolapsed into the vagina immediately after the rupture of the membranes and the pulsations were weak. Immediate delivery was considered urgent and accordingly a podalic version was performed under spinal anesthesia, employing 100 mg. of procaine and a living normal child was delivered despite the fact that the cord was not pulsating at birth. The implantation of the placenta was low and this factor probably explains the prolapse of the cord. There were no cervical or perineal tears and the placenta was expelled in a few minutes by simple expression.

Mother and baby left the hospital on the ninth post-partum day in good condition.

CASE 5.—Mrs. C. M., aged 22, gravida i, para o. Patient was admitted to the hospital because of pregnancy complicated by subacute bacterial endocarditis.

Her expected date of delivery was on August 30, 1943. She went into labor on July 3, and for fear of producing depression and asphyxia in the premature child no sedation was given the mother. Soon after initiation, labor became strong and the patient was uncooperative and "fagging" herself out.

The cervix was then two fingers dilated. One hundred mg. of procaine were administered by the spinal route and within one minute manual dilatation attained full cervical dilatation. The membranes were then ruptured artificially and a living premature child weighing 3 pounds and 5 ounces was delivered by low forceps.

The patient stood the ordeal well and was very grateful for the immediate relief from pain accorded by the spinal anesthesia. On the tenth post-partum day she was transferred to the medical service and the child left the hospital in good condition on the forty-second day. The mother is still alive at the time of this writing.

### Discussion

It can be demonstrated pharmacologically and certainly clinically that spinal anesthesia relaxes the cervical muscles so that the cervix can be easily dilated, and at the same time, it causes contraction of the corporeal muscles. This latter action greatly limits the blood loss.

While it is true that the cervix can be manually dilated under general anesthesia, nevertheless the advantages gained by employing spinal anesthesia make it the anesthetic of choice in the type of cases under consideration. Under spinal anesthesia, the dilatation of the cervix can be more easily performed, the child practically always cries



spontaneously, obviating the need for resuscitation and the blood loss is usually far less than under general anesthesia.

Due to the fact that every case requires delivery by a major obstetric procedure, it follows that this technique should be employed only by thoroughly experienced obstetricians for otherwise the results will not only be unsatisfactory but in many cases truly tragic.

### Summary

The employment of spinal anesthesia in obstetric patients in whom immediate delivery is indicated is advocated and discussed. Five illustrative cases are described.

### Conclusions

In instances where haste is indicated and cephalopelvic disproportion does not exist, delivery under spinal anesthesia is both feasible and very satisfactory.

Every case subjected to spinal anesthesia requires mastery of obstetric operative procedures, therefore patients anesthetized by the spinal route should be delivered by thoroughly trained and experienced obstetricians.

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## PREGNANCY AT TERM IN PROLAPSED UTERUS WITH PROLAPSE OF CORD\*

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**P**ROLAPSE of the uterus at or near term is rare. In the Bronx Hospital from January 1, 1938, to November 1, 1943, this case is the only one in 15,696 deliveries. Keettel<sup>1</sup> had one case in 13,000 deliveries in a period of over 14 years. From another hospital he was able to report another case which occurred in 2,000 deliveries over a period of 10 years. This led him to analyze 170 reported cases, 137 of which were collected before 1901 by Franke, Seitz and Andrews. Palmer Findley<sup>2</sup> added 10 more cases in 1911, and 23 other reports, including the three he reports, have appeared since then. Most of the cases that have gone to term showed only an elongated, hypertrophied and edematous cervix. Up to the seventh lunar month cases have been reported with complete precedents, but with a full-term fetus this is hardly possible. Most of Keettel's analyzed cases occurred in multiparas.

The condition seems to have little effect on fertility and pregnancy occurred in spite of marked chronic endocervicitis. Early abortion (21 per cent) is relatively frequent. Findley advises plastic repair at this early stage without interruption of pregnancy. It was found that, because the uterus rose out of the pelvis after the fourth or fifth month of pregnancy, thus pulling the cervix into the vagina, there was less tendency to spontaneous abortion. Therefore, Franke and Seitz, in their earlier cases, recommended the use of a pessary until the uterus was enlarged and the cervix drawn upward. Andrews<sup>2</sup> feels the incidence of breech presentations was increased.

The operative incidence reported by Keettel was high. The most common method of delivery, outside of spontaneous deliveries (45.7 per cent), was the use of forceps (27.1 per cent), after Dürrssen's incisions (29.3 per cent). Version and extraction (4.3 per cent), craniotomy (7.8 per cent), and cesarean section (one case of the Porro type) were used only occasionally. The fetal death rate was high (22.1 per cent). Maternal mortality was also high (6.3 per cent), nearly all due to sepsis.

The treatment of this condition was formerly radical, but has in recent years become conservative.

### Case Reports

Mrs. D. L., aged 39, gravida v, para iv, came to the prenatal clinic for the first time on July 27, 1943. At this time she stated her last menstrual period was February 1, 1943, and her expected date of confinement was figured as November 8, 1943.

Her past medical and surgical history was negative. She had four children, the oldest eighteen and the youngest two years of age. Their birthweights were 8, 9, 9, and 7 pounds and 10 ounces, respectively.

\*This case report was made available through the courtesy of Dr. Meyer Rosensohn, attending Obstetrician, Bronx Hospital, New York, N. Y.

†Presented at a meeting of the Section of Obstetrics and Gynecology of the New York Academy of Medicine, December 28, 1943.

Physical examination revealed the heart and lungs negative. The pelvic measurements were ample. The abdomen showed a five months' pregnancy, the height of the fundus above the symphysis being 21 cm. Vaginal examination revealed a cystocele, rectocele, and a first degree uterine prolapse. Urine and Wassermann tests taken at this time were negative.

The prenatal clinical course was uneventful with her blood pressure around 105 systolic and 60 diastolic.

According to her history, on the night of October 19, 1943, she felt something protruding from the vagina, but she went to bed, and did not enter the hospital until 10:35 A.M. of the following day. There were no edema and no pains. The abdomen revealed a pregnancy almost at term, breech presenting, with the back to the right and anteriorly. No fetal heart sounds were heard. Projecting from the vagina for a considerable distance were the cervix and the uterus, and protruding from the cervix was a nonpulsating cord. In the delivery room, after sterile precautions, the protruding mass was redeposited into the vagina. At this time the cervix was dilated  $1\frac{1}{2}$  fingers and a footling presentation was made out. That afternoon, when seen by the attending obstetrician, the temperature had risen to 102° F. Noting the absence of pulsation of the cord, and the length of time it had been prolapsed, no interference at this time was advised. Two grams of sulfadiazine were given immediately, followed by one gram every four hours. Two ounces of easter oil were also given, with the hope of inducing labor.

By 9:00 P.M. that evening, the patient was having moderate contractions, but because of her temperature 1,000 c.c. of 5 per cent glucose were given intravenously, and she was given sedatives. At 7:15 A.M. the following morning, after a 10 $\frac{1}{4}$ -hour labor, the patient delivered a stillborn breech, R.S.A., female, weighing 7 pounds. There was no laceration. Following the delivery the patient had a chill, and the temperature rose to 103.6° F., which dropped to normal by 4:00 P.M. that afternoon.

The laboratory examination showed urine: specific gravity 1.020, sugar and albumin negative, acetone 2 plus, diacetic acid 1 plus, occasional red blood cells, and 4 to 5 white blood cell per high power field. Blood count showed hemoglobin 92 per cent, red blood cells 4,230,000, white blood cells 23,100, polys 80 per cent, band forms 7 per cent, lymphocytes 13 per cent and toxic granulation of the neutrophils. Blood culture was sterile after 144 hours of incubation.

For the next few days the temperature fluctuated around 100° F., but was back to normal on the fifth day postpartum. Except for a slight cough, but with no signs in the chest, the puerperium was uneventful, and the patient was discharged on the tenth day post partum. She was sent to the gynecological clinic, to be later referred to the hospital for operation.

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# A CASE OF PSEUDOHERMAPHRODISMUS FEMINUS EXTERNUS WITH UTERUS DIDELPHYS, IMPERFORATE ANUS AND VAGINA

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**C**ONGENITAL malformations of the urogenital system are adequately described in most obstetric textbooks. The case presented is interesting because of the inability to determine the sex of the infant before death and the bizarre combination of anomalies which were found at autopsy.

Mrs. V. H., aged 19, primipara, was first seen in the prenatal clinic of the Station Hospital, April 16, 1942. Her last menses occurred Dec. 5, 1941, and the expected date of delivery was Sept. 12, 1942. Examination revealed the uterus enlarged to 20 weeks' gestation. The pelvic measurements were normal and the rest of the examination was essentially negative. The prenatal course was normal in every respect and patient went into labor Sept. 16, 1942. In 4 hours the baby was spontaneously delivered after a midline episiotomy. The puerperium was uneventful and the mother was discharged from the hospital on the tenth day. The baby weighed 8 pounds and cried at once.

Physical examination of the baby revealed congenital anomalies. The rectum was absent nor was there any dimple to show the presence of a blind pouch. The genitals were distinguished by two normal looking labia majora. There were no labia minora. The vaginal opening was absent nor was there any evidence of a hymen. The clitoris was hypertrophied to four times the normal size, resembling a penile organ. Just below it was a longitudinal urethral opening and below this was a small pendulous serotal-appearing structure. Testes were not palpable here nor in the groin. The sex could not be determined definitely.

*Course.*—The baby outwardly appeared in good condition. Urine passed from the urethra. Occasionally gas was expelled through the same orifice. Seventeen hours after delivery, under local anesthesia, the perineum was explored surgically by Major T. R. Hannon, M. C., but no rectal pouch could be found. Thereupon a simple left-sided colostomy was performed by bringing a loop of sigmoid up through the lower left rectus muscle and suspending it in position with a glass rod under the intestinal loop. Twenty-four hours later the colostomy loop was opened by a live cautery and bowel function began through this opening. The baby took artificial feedings well and was discharged from the hospital on the tenth day in good condition, weighing 7 pounds 14 ounces.

On October 5, 1942, nine days after leaving the hospital, the baby was readmitted, acutely ill with a history of vomiting, fever, and increasing abdominal distention. For the past 24 hours no urine had been passed and the fecal drainage from the colostomy had almost ceased. Physical examination revealed an acutely ill infant with marked abdominal distention. There was a firm, fixed mass in the right lower quadrant, pressure on which caused urine to flow from the urethra. X-rays made after injection of skiodan into the loops of the colostomy failed to reveal any definite evidence of obstruction. X-rays of the genitourinary system with retrograde skiodan injection were

suggestive of a multicystic kidney on the left side. No kidney or ureter was visualized on the right side. The colostomy was irrigated with saline solution and profuse amount of fecal matter was discharged. The abdominal distention subsided. However, the urinary suppression continued, the baby became toxic, vomited persistently and died 36 hours after admission, 21 days after birth.

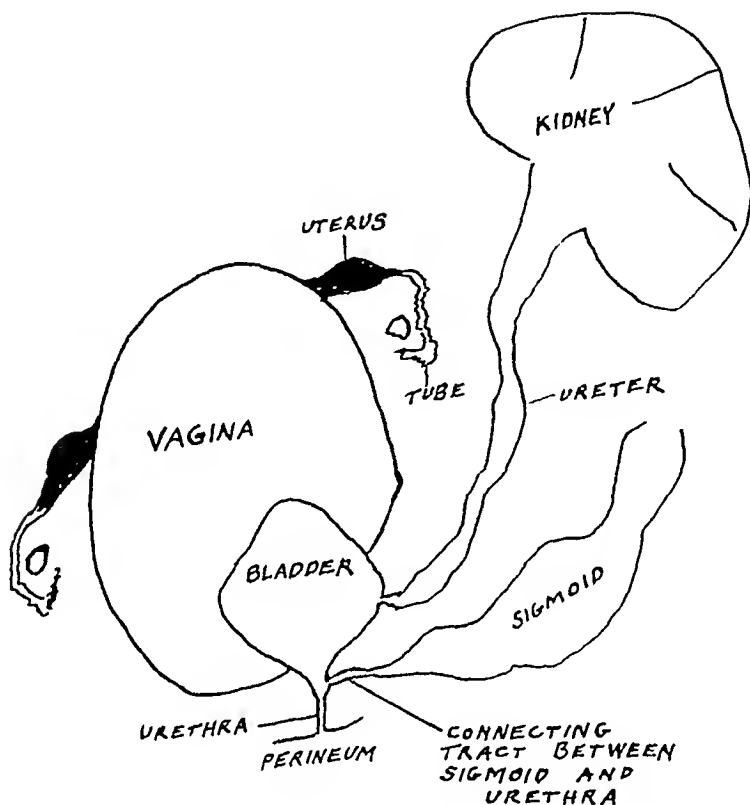


Fig. 1.—Diagrammatic representation of congenital anomalies.

*Autopsy.*—The following is an excerpt of a complete postmortem examination done by Captain George M. Hass, M. C.: Terminal pneumonia and the presence of a colostomy was noted. The rectum terminated in a narrow tract about 1 centimeter long and 3 millimeters in diameter which communicated with the posterior urethra. The right kidney and ureter were absent. The left kidney and ureter were dilated and showed evidence of recent infection. The bladder was normal except for absent right ureteral orifice. Posterior to the bladder was a large cyst about 15 centimeters in diameter, filled with foul smelling yellowish purulent material under tension. On each of the upper and lateral aspects of the cyst was a uterus, tube and ovary. Below, the cyst reached to about 1 centimeter from the skin of the perineum at the vulval region where the vaginal introitus should have been.

*Final Diagnosis.*—1. Acute pyelonephritis left kidney due to congenital connection between sigmoid colon and posterior urethra,

2. Hydronephrosis left kidney,

3. Uremia, terminal, and

4. Congenital anomalies: absence of right kidney and ureter; uterus didelphys; imperforate anus; imperforate vagina; pseudohermaphroditism feminus externus.

## TUBAL PREGNANCY IN A TUBERCULOUS FALLOPIAN TUBE

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THE coexistence of tuberculosis and ectopic gestation in the Fallopian tube appears to be a very rare occurrence. In 1939, Stevenson and Wharton<sup>1</sup> reviewed the literature of the subject and noted that exclusive of their own single case, only 8 cases had been previously reported. They believed that their case was the first proved case reported "from the English-speaking world." It was also the first case in the 47 years of the existence of the gynecologic and pathologic laboratories of the Johns Hopkins Hospital—a period in which 402 cases of tuberculous salpingitis and 516 of tubal pregnancies had been observed.

In 1940, apparently as a result of a more thorough search of the literature, Bland<sup>2</sup> assembled 32 cases and added one of his own. This represented the only such case which had been observed in the Jefferson Medical College between 1907 and 1939, during which period some 55,000 surgical specimens had been examined. Of these, 209 represented tubal pregnancies and 38, tuberculous salpingitis. Since 1940, some four additional cases have been reported in the American and in the continental literature.

Our patient, S. G., aged 27, was first admitted to the Mount Sinai Hospital six years ago—3/27/36, with a three months' history of painful, bloody urination. Some weight loss had occurred. Physical examination disclosed a patient in apparent good health with no important findings, except a soft systolic murmur at the apex. There was no history of tuberculosis in the family or any past history of tuberculosis. An examination of the chest disclosed no clinical evidences of active tuberculosis. X-ray of the chest was normal. Urine from the right kidney showed acid-fast organisms, that from the left showed none. An occasional acid-fast rod was found in the feces. An intravenous urography done prior to operation disclosed a moderately enlarged right kidney, whose lower pole showed soft masses and a small amount of mineral deposits, as is occasionally seen in tuberculosis. The sputum at no time showed tubercle bacilli. A right nephrectomy was done. Histologic examination disclosed a tuberculous pyelonephritis with abscess formation. The patient was discharged after a month's stay, in apparent good health.

The patient was readmitted on 4/6/41, five years later, with a history of lower abdominal pain localized in the right abdomen which had persisted for the previous two days. In addition, during this period, vaginal bleeding had started. Her last menstrual period was 2/24/41. The patient had married since her discharge from the hospital. Urine analysis on this occasion showed 1 to 2 W.B.C. per h.p.f. and no R.B.C. The hemoglobin and red blood cell count were normal. A diagnosis of tubal pregnancy was made and on the following day, under spinal anesthesia, a right salpingectomy and appendectomy were performed. At operation, free blood was found in the peritoneal cavity and bleeding was noted from the fimbriated end of the right tube.

This tube was larger than normal and appeared indurated in its mid-portion. X-ray of the chest, done one week postoperatively, was entirely negative.



Fig. 1.—Section of Fallopian tube showing matted villi and tuberculous process. Note giant cells and tubercles. ( $\times 100$ .)



Fig. 2.—Section of Fallopian tube showing decidual tissue and chorionic villi. ( $\times 100$ .)

*Pathologic Findings.*—The specimen consisted of a Fallopian tube measuring 6 by 1.3 cm. At its fimbriated extremity, a small amount of firm, dark-brownish blood was present. Its serosal surface was reddish-purple and smooth. Its wall was greatly thickened, considerably narrowing the lumen. The lumen at the uterine end contained thin, red blood. The fimbria were large. Microscopically, two processes were present—a productive tuberculous salpingitis (Fig. 1) and areas containing chorionic villi and decidual tissue (Fig. 2). Endometrial tissue passed three days following operation consisted of hemorrhagic, moderately inflamed decidua showing no evidences of tuberculosis. (Fig. 3.)

Her postoperative course was good. About 15 days after admission, she showed signs of a psychosis and insisted upon being discharged.



Fig. 3.—Endometrial tissue showing decidual reaction and absence of tuberculosis. ( $\times 100$ .)

### Discussion

It is believed that the rarity of the association of tubal tuberculosis and pregnancy is probably in some measure due to the blocking of the lumina of the tubes to the spermatozoa and ova by the tuberculous process. Even should this obstacle be circumvented, it would appear that the nidation in the uterus is usually unsuccessful since in the series of 402 cases of tuberculous salpingitis studied by Stevenson and Wharton,<sup>1</sup> there was an 85 per cent incidence of associated tuberculous endometritis. Hence, the well-known association of sterility with tuberculosis of the genital tract. While there have been reported instances of conception in cases of tuberculous endometritis, probably as the result of the clearing of the process by successive curettements, there does not appear to be present the same opportunities for the clearing of the tubal tuberculosis. However, it should be noted that the lumen of the tube in tuberculous salpingitis may remain open to a slight



degree in the early stages of the disease and even in advanced cases. Since histologically the tuberculous process is often focal, there exists the setting for the rare occasion when the fertilized ovum may nidate and mature in an uninvolved or only slightly involved area. However, even should such a nidation be successful, because of the scarring brought about by the tuberculous process with the consequent diminished tubal elasticity, rupture usually supervenes before the fetus attains an appreciable size.

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**Tietze, Christopher: Differential Reproduction in the United States—Paternity Rates for Occupational Classes Among the Urban White Population, *Am. J. Sociology* 49: 242, 1943.**

This study is based on a portion of the National Health Survey of 1935 to 1936. To study and report the relationship between paternity and occupation is the purpose of the author. Occupational groups are divided into the professional, business, skilled and semiskilled, unskilled, and miscellaneous which includes farmers, farm laborers, etc. The highest paternity rate was in the skilled and semiskilled group, business group was next; unskilled, professional and miscellaneous followed in that order. The net paternity rate for the four classes was professional 0.68, business 0.69, skilled and semiskilled 0.86, unskilled 0.89. When these groups were studied on the basis of education it was found that the highest net paternity rate occurred in men who had seventh grade education or less (0.97), eight grade (0.86), High School (0.68), and college (0.52). On the basis of income the reproductive rates were: \$3,000 and over 0.42; \$2,000 to \$3,000, 0.61; \$1,500 to \$2,000, 0.70; \$1,000 to \$1,500, 0.86; under \$1,000, 1.17.

Considerable attention is given to classifying and breaking down the paternity rate into 3 subgroups and also in contrasting paternity rate with reproduction rate and correlating the two. These involve technical factors which should be of very material value to the sociologist or statistician but for the average physician it is rather difficult to analyze.

WILLIAM BICKERS.

## SUCCESSFUL BRONCHOSCOPY FOR ATELECTASIS IN A SIX-HOUR-OLD INFANT

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*(From the Buffalo General Hospital)*

**B**RONCHOSCOPIC examination in newborn infants is a recognized procedure but the use of the bronchoscope immediately after birth for the treatment of atelectasis is apparently rare. The following case is reported for two reasons: (1) the fact that the infant was but six hours old at the time of examination, and (2) to emphasize the value of immediate bronchoscopy in cases of atelectasis in newborn infants.

Delivery of the baby by one of us (D. D. D.) was by Porro-cesarean section because of a ruptured uterus. The throat was immediately aspirated with the tracheal catheter and the infant cried and seemed normal. Shortly thereafter, however, intermittent cyanosis developed. Examination showed marked retraction of the right chest with absence of breath sounds and dullness to percussion. The heart findings were normal. There were no signs to suggest cerebral hemorrhage but vitamin K was given. A diagnosis of atelectasis of the right lung was made. Treatment with carbon dioxide and oxygen inhalations was of no avail, nor did lying on the unaffected side relieve the condition.

The infant was well developed in every way and showed no abnormalities other than the atelectasis. It was felt that if the atelectasis was due to a blocking of the bronchus by mucus, bronchoscopy might be of help. Accordingly, a bronchoscope for newborn infants was passed by one of us (H. E. B.). The infant was then six hours old. A considerable quantity of thick, yellow secretion was aspirated from the trachea and a small amount from the right bronchus. The right bronchus seemed to be collapsed; there was a little chink at the carina and below this the membranes were quite red. Immediately following aspiration, aeration of the right lung was audible through the stethoscope, the right chest expanded to equal the expansion of the left side, and the breathing became normal on both sides. The baby's condition remained good for the duration of its hospital stay and when discharged, the baby seemed to be entirely normal.

Two months later an x-ray film of the chest, taken because of the development of a bronchopneumonia from which the baby made a rapid recovery, showed apparently complete expansion of the lung. The roentgenologic report stated "there is bronchopneumonia throughout the right lung which is completely expanded."

At the age of three and one-half months a fatal influenzal meningitis and bilateral otitis media developed. Autopsy was performed at the Children's Hospital in Buffalo by Dr. K. Terplan who found at that time, diffuse edema and slight atelectasis of both lungs, hyperplasia of the thymus and lymph glands, and moderate enlargement of the spleen.

The final unhappy outcome in this case does not alter the fact that the prompt use of the bronchoscope a few hours after birth undoubtedly saved the infant's life at that time. The extent to which any possible residual atelectasis may have contributed to the illnesses which followed, we do not know. We are reporting the case in the hope that it will stimulate interest in the use of the bronchoscope as a lifesaving measure in cases of atelectasis in newborn infants.

# Department of Statistics

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## RUPTURE OF THE UTERUS

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THE reported incidence of rupture of the uterus varies considerably. Stander<sup>1</sup> reports 12 cases in a series of 27,125 consecutive deliveries, or one in every 2,260 labors at New York Lying-in Hospital. In a review of 51,571 cases from the combined services of the University of Maryland and the Baltimore City Hospitals, Reese and Linn<sup>2</sup> found this accident to occur once in every 1,516 confinements. However, the highest incidence of rupture of the uterus which the authors have been able to find is that reported by Whitacre and Fang<sup>3</sup> from Peiping Union Medical College: among 11,500 obstetric admissions, there was one rupture in every 220 cases. Irving<sup>4</sup> states that rupture of the uterus has been treated once in every 1,959 deliveries at Boston Lying-in Hospital.

Herewith is reported a series of 23 cases of rupture of the uterus, occurring in the 16-year period from 1925 to 1941. This group of patients includes all cases of this accident seen at University Hospitals of Cleveland (Maternity Hospital) during this period of time. In this 16-year period 34,295 deliveries were conducted at Maternity Hospital, and 29,096 patients were confined at home by the Maternity outpatient service of Western Reserve University, thus giving a grand total of 63,391 obstetric cases. Rupture of the uterus, therefore, has been treated once in every 2,756 deliveries seen on this obstetric service.

*Age.*—The ages of the patients varied from 19 to 38 years; the mean age was 28.4 years. Five of the 23 patients were 36 years of age or older.

*Parity.*—In the entire group there were only three primiparas, the average parity being 3.6. It is well known that multiparas experience this accident much more frequently than do primiparas. Schumann<sup>5</sup> states the ratio to be 12:1; the ratio in our series, however, was 6.6:1.

*Etiology.*—The causative factors of rupture may best be considered by dividing the cases into the following five groups:

1. *Previous Cesarean Section.*—Rupture of a remote cesarean scar was the causative factor in 13, or 56 per cent of the 23 cases. All of the previous sections were of the classical type; no case of rupture following laparotrachelotomy was encountered in this series. Six of the patients had had 2 or more cesarean sections, whereas 7 patients had had but one previous section. The mean number of previous sections was 1.5. One patient had had 3 previous sections.

TABLE I. ETIOLOGIC FACTOR ASSOCIATED WITH 23 CASES OF RUPTURE OF THE UTERUS

ETIOLOGIC FACTOR	NO. CASES	PER CENT
Cesarean scar (classical)	13	56 plus
Podalic version	6	26
Oxytocic agent	1	4
External trauma	1	4
Undetermined (spontaneous intrapartum)	2	8

All of the ruptures occurring in the previous section group were spontaneous in onset. Five, or 38 per cent of the 13 cases occurred before the onset of labor, but all were at or near term, excepting one which happened in the eighth month of gestation. The other cases (68 per cent) occurred after the onset of labor, which varied from one to twelve hours, and all of these individuals were at or near term.

In fairness to the classical operation, it should be stated that the dictum "once a cesarean, always a cesarean" had not been followed at this clinic until approximately ten years ago, since which time laparotrachelotomy, rather than the classical operation, has been the most frequently performed type of abdominal delivery. Prior to the last decade, any number of patients were allowed vaginal delivery after previous section, provided, of course, the indication for section had been a temporary one, such as placenta previa, or toxemia of pregnancy. Whenever pelvic contraction had been the indication for the original section, naturally enough all subsequent pregnancies were terminated by elective section. It has been in the last decade only that the policy of doing elective section on all previous cesarean patients has been followed in all cases, regardless of the nature of the indication for the original abdominal delivery. These facts are related so that conclusions drawn from a comparison of the classical versus the low cervical operation will not be misleading.

2. *Internal Podalic Version*.—This procedure accounted for 6, or 26 per cent of all the cases of uterine rupture. The indication for version was persistent vertex occipitoposterior position in 5 of the cases, and compound presentation (arm and leg) in the sixth case. Version was carried out successfully in 3 of the 6 cases, but failed in 2 others, in one of which a contraction ring was recognized. In one case included in this category, version itself was not actually attempted, inasmuch as the uterus was found to give way when the operator introduced his hand into the uterine cavity.

3. *Oxytocics*.—The administration of an oxytocic agent (crude ergot) accounted for one case, or 4 per cent of the total series. That was a para iv, aged 37 years, who had been given a hypodermic injection of ergot by a midwife to stimulate labor pains. The patient was admitted later to Maternity Hospital for treatment. Laparotomy revealed a complete rupture at the level of the internal os, which had dissected the peritoneum from cecum to sigmoid. There was remarkably little bleeding, and minimal shock. Curiously enough, none of the major vascular supply to the uterus had been implicated by the rupture. Supracervical hysterectomy and salpingectomy were followed by complete recovery.

Inasmuch as pituitary extract is practically never used on this obstetric service until the third stage of labor, it is understandable how no case of rupture due to this agent is reported in this series of cases.

4. *External Trauma*.—A fall on the abdomen was the precipitating factor in one patient, or 4 per cent of the series: This was a 30-year-old-

primigravida, who was admitted to Maternity Hospital in her seventh month of pregnancy, because of hydramnios accompanying twin pregnancy. The patient was put to bed and given barbiturates to relieve the discomfort due to distention. While under the effects of barbiturates, the patient got up out of bed and fell prostrate on the floor, where she was found in shock. Laparotomy revealed both twins free in the abdomen; one of the fetuses was stillborn, whereas the other died shortly after delivery. Supracervical hysterectomy was performed, and the patient recovered after a convalescence complicated by intestinal obstruction and pelvic cellulitis.

Doubtless, the twin pregnancy with its accompanying hydramnios was an etiologic factor in the case just cited. In retrospect, it probably would have been better to have relieved the hydramnios by artificial rupture of the membranes.

5. *Undetermined Etiology.*—Two cases of spontaneous intrapartum rupture of undetermined etiology were seen. The first patient in this group was a 22-year-old para iii who died almost immediately after the spontaneous delivery of a 7-month stillborn. Autopsy revealed a complete rupture; unfortunately, nothing is known about the previous obstetric and gynecologic history of this patient. The second patient, a 34-year-old para iv, had an easy labor, and low forceps delivery, but suddenly went into profound shock, and expired during laparotomy, despite 2,350 c.c. of whole blood, and 500 c.c. of serum. Operation revealed an incomplete tear in the lower uterine segment, 6 cm. in length, and located below the bladder-flap. The cause of the rupture in this case, too, is shrouded in mystery. The authors are inclined to the belief that perhaps an old cervical laceration might have given way during labor, with extension of tear into the lower uterine segment, as suggested by Gordon and Rosenthal.<sup>6</sup> No other explanation as to why these two uteri ruptured spontaneously seems likely. Both patients were multiparas; both had easy labors; and both had uncomplicated deliveries. One can only surmise that the cervix was at fault.

*Degree of Rupture.*—Of the 23 cases, 17, or 74 per cent were complete ruptures, that is, extended through the peritoneal covering of the uterus; on the other hand, 6, or 26 per cent were partial ruptures, consisting of subperitoneal extension of the laceration, with hematoma-formation between the leaves of the broad ligament. All but 2 of the cases resulting from previous cesarean section were of the complete variety. Half of the version cases were complete; half were partial.

TABLE II. FREQUENCY OF COMPLETE VERSUS PARTIAL RUPTURE

GROUP	COMPLETE		PARTIAL	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Cesarean scar	11	85	2	15
Version	3	50	3	50
Oxytocic	1	100	0	0
External trauma	1	100	0	0
Undetermined	1	50	1	50

The diagnosis of rupture of the uterus was made in one near-term secundipara who complained of lower abdominal discomfort for 60 hours; examination showed a bulging fluctuant mass, 2½ cm. in diameter, presenting under the lower midline scar. This patient experienced a stormy convalescence after her first cesarean section. The

preoperative diagnosis of membranes herniating through a defect in the anterior uterine wall was confirmed at laparotomy.

A Bandl contraction ring was diagnosed in 2 patients who proved later to have ruptured uteri. In both instances, internal podalic version was attempted in the face of a contraction ring, an absolute contraindication for podalic version. In 2 other cases undue resistance was encountered in executing the version, due to inadequate uterine relaxation, a *sine qua non* for successful version. In the fifth rupture due to version, the uterus, which previously had seemed adequately relaxed, "clamped down" during version, with resulting rupture. In the sixth case, as the operator's hand was introduced to perform version, a rent in the lower uterine segment was recognized. The indication for podalic version in 5 of the 6 cases was high persistent vertex occipitoposterior position; in the other case the indication was compound presentation.

### Treatment

Operative treatment was carried out in 22 of the 23 patients. The only one who received no surgical treatment was a patient who had sustained a spontaneous intrapartum rupture of undetermined etiology; death ensued before blood transfusion, etc., could be arranged. Supracervical hysterectomy (7 times) and Porro cesarean section (6) were the most commonly performed surgical procedures. Simple repair of laceration was done three times. Each of the other operative procedures, vide infra, was done once each.

TABLE III. OPERATIVE PROCEDURES PERFORMED UPON 22 PATIENTS

OPERATION	NO. CASES	DEGREE RUPTURED	
		COMPLETE	PARTIAL
Supracervical hysterectomy	7	6	1
Porro section	6	4	2
Repair laceration	3	3	0
Supracervical hysterectomy and salpingectomy	1	1	0
Supracervical hysterectomy and salpingo-oophorectomy	1	0	1
Panhysterectomy	1	0	1
Classical cesarean and tubal ligation	1	1	0
Laparotrachelotomy	1	0	1
Laparotomy	1	1	0

### Maternal Mortality

Of the 22 patients operated upon three sustained immediate operative deaths, i.e., expired during operation; one succumbed to peritonitis

TABLE IV. TABULATION OF MATERNAL MORTALITY

OUTCOME	NO. CASES	PER CENT
Immediate intrapartum death	1	4 plus
Expired during or immediately after operation	3	13
Succumbed to peritonitis	1	4 plus
Recovered	18	78
Total	23	100

on the fifth postoperative day. In all, 18 patients survived, thus giving a gross mortality of 22 per cent, consisting of an immediate surgical mortality of 13 per cent, and a postoperative mortality of 9 per cent.

### Analysis of Fatal Cases

CASE #16-222.—Para ii, aged 20 years. One previous cesarean section for contracted pelvis and disproportion. In active labor with floating head for 8 hours, before section was started. Just prior to operation patient went into shock, and expired during laparotomy. Free blood in peritoneal cavity. Saline infusion was the only supportive treatment given (1926).

*Comment:* Had operation not been so long delayed after the onset of labor, rupture probably would not have occurred. Moreover, whole blood and/or plasma would have improved tremendously the chances of survival after the onset of shock.

CASE #19-043.—Para vi, aged 28 years. Two previous cesarean sections for mitral stenosis. History of constant pain in left lower abdomen for 18 hours before section was started. Much free blood was encountered as soon as abdomen was opened, whereupon the patient went into immediate and profound shock, expiring 20 minutes after incision had been made. No antishock treatment at all (1927).

*Comment:* Earlier operation, and modern antishock therapy, as practiced today, would probably have reversed the outcome.

CASE #27-346.—Para vii, aged 37 years. Rupture occurred during attempted version for high persistent vertex occipitoposterior position, despite the presence of a contraction ring (1931). Death occurred on the fifth postoperative day from peritonitis and paralytic ileus. Hysterec-tomy had been done for complete rupture.

*Comment:* The local use of sulfonamides, as practiced today, plus parenteral sulfonamides, and Miller-Abbott tube following operation would be in order in the management of such a case today.

CASE #39-534.—Para iii, aged 22 years. Rapid labor with severe pains, followed by the spontaneous delivery of a 7-month stillborn fetus. Profuse and fatal postpartum hemorrhage, although fundus contracted firmly at regular intervals. Intravenous saline and acacia solution (400 c.c.) were the only supportive treatment given (1936). Patient expired before transfusion could be arranged. Nothing is known about the previous obstetric and/or gynecologic history.

*Comment:* The etiology is obscure. The most likely cause seems to be the possibility of the giving way of an old cervical laceration, with extension of tear into the broad ligament. Three such cases have been reported by Gordon and Rosenthal.<sup>5</sup> The precipitous character of the labor should have been slowed down by the timely use of analgesics and anesthetic agents. It is readily understandable how an old cervical laceration, especially one which had escaped notice, or for other reasons had not been properly repaired at the time of a previous delivery, could have given way during a subsequent labor, particularly during one characterized by rapid dilatation of the cervix. Extension of such lacerations, as suggested by Gordon and Rosenthal,<sup>6</sup> may explain the spontaneous rupture occurring in the apparently normal uterus of the "grande multipara."

CASE #53-283.—Para iv, aged 34 years. Easy labor (16 hours); low forceps delivery, followed by profuse and persistent postpartum hemorrhage, which continued unabated despite packing and intravenous ergotrate. Notwithstanding 2,850 c.c. of whole blood and serum, this patient expired during operation, which disclosed a partial rupture of the lower uterine segment (1941).

*Comment:* Unfortunately nothing is known of the past obstetric history of this patient. The only tenable explanation of rupture would seem to be the possibility of the giving way of a scarred cervix, with extension of laceration into the lower uterine segment.

### Fetal Salvage

Of the 24\* fetuses 14 were stillborn; 9 survived, and there was one neonatal death.

TABLE V. TABULATION OF FETAL SALVAGE

OUTCOME FOR FETUS	NO. CASES	PER CENT
Stillborn	14	58
Survived	9	38
Neonatal death	1	4
Total	24	100

### Summary

1. A series of 23 cases of uterine rupture has been reviewed. The etiology, clinical picture, treatment, and prophylaxis of this obstetrical catastrophe have been discussed.

2. All patients who experienced rupture of the uterus following cesarean section had had the classical operation; no instance of rupture subsequent to laparotrachelotomy was encountered in this series.

3. Six cases of rupture were attributed to internal podalic version and breech extraction. The conditions essential for safe and successful version have been stressed.

4. The possibility of old cervical lacerations giving away during labor has been suggested as a not unlikely explanation for certain cases of rupture in multiparas, in the absence of more overt causative factors.

5. Of the 23 mothers, 18 survived. However, with the more modern methods of treatment available today, probably 4 of the 5 fatal cases would not have succumbed.

6. The fetal salvage was 38 per cent.

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\*From the group of 23 mothers there were 24 fetuses, due to the fact that one mother had twins.



## Special Article

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### CONTRAINDICATIONS AND CAUTIONS IN THE USE OF CONTINUOUS CAUDAL ANALGESIA\*

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CONTINUOUS caudal analgesia is a natural outgrowth from a combination of the principles of several procedures practiced in anesthesia during the last four decades. Sicard and Cathelin of France in 1901, first used the sacral hiatus as the approach to the extradural space for their injections of cocaine solutions in order to block the nerves transmitting pelvic pain in the specialty of urology.

Stoeckel (1909), and later Schlimpert (1911) of Germany, first applied this method for the relief of pain in obstetrics. They utilized the drug novocain which had recently been prepared by the chemist Einhorn to replace the more toxic cocaine. Their method completely relieved the pains of delivery for a period of thirty minutes to one hour in suitable cases.

In 1921, Pagés of Spain made use of the extradural space for nerve block in surgery through the interspinous lumbar approach. Dogliotti of Italy further refined this technique and demonstrated its use as the method of anesthesia for surgery of the lower two-thirds of the body.

In America Meeker, Bonar, Campbell, Rucker, Thompson, Labat, Lundy, Sword, Baptisti, Odum, Lahman, and Mietus made valuable contributions to the art of single-injection caudal analgesia and anesthesia in the various branches of medicine, surgery, and obstetrics. Grafanino dramatically achieved the same results in obstetrics by using the approach of Pagés and Dogliotti.

All these men recognized the advantages and hazards of the single injection to achieve an effective nerve block for a very limited space of time depending upon the pharmacologic effect of the drug used. They all stressed the contraindications and complications of their experience in warning physicians to safeguard the patient against the hazards attendant upon its use and misuse.

Recently (in 1941) the author, in collaboration with Edwards and Southworth, cognizant of the advantages of Lemmon's new refinement of continuous spinal anesthesia, introduced continuous caudal analgesia for both surgery and obstetrics. Almost immediately both medical and nonmedical writers of the lay press seized upon the scientific reports

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to the profession of this work with such an acclaim and "blast of trumpets" that both the lay public and the bystanding physician have become the victims of distortions, misrepresentations, and literary salesmanship. The result has been a dangerous demand on the part of the obstetric patient for a method of pain relief that is still in the developmental stage and a reactionary defense on the part of the physician who has been forced to deflate the enthusiast with the sharp edge of conservative caution.

The fact remains that more than one hundred lay articles have appeared in the press from the pens of authors who have never once seen continuous caudal analgesia nor are they familiar with obstetrics. As a result, thousands of women are led to believe that continuous caudal analgesia can be purchased across the counter in every maternity section of all hospitals as a panacea and a happy detour from the usual experiences of childbirth.

On the developmental side of the problem, one hundred and sixty clinics have already reported more than 30,000 births managed with this technique. This method has been used in more than half the countries of the world. Apparently, many more thousand attempts have been made with some mixed results in instituting the technique. The promised "dramatic relief of all pain" attendant upon the act of childbirth has not been fulfilled in all cases in both unskilled and skilled hands.

I believe that continuous caudal analgesia, when properly administered, will completely relieve the pains of labor and delivery. The pain relief of this procedure receives a disproportionate emphasis when reviewed against the background of the vigor of the first cry of the newborn infant, uninfluenced by narcotization and anesthesia, the diminished third-stage blood loss, and the rapidity of post-partum convalescence.

Nevertheless, the limitations of the technique should be evaluated; it is not a procedure to be used in the home and in the poorly staffed hospital. This eliminates more than 70 per cent of American births from consideration. In addition, we estimate that 40 per cent of parturients delivered in well-staffed maternity units present contraindications prohibiting its successful use in the early experience of any clinic. Thus, if every hospital in the United States utilized this form of obstetric management in every suitable case, only 12 per cent of women could benefit from this form of pain relief. The truth remains that not more than one hospital in ten is utilizing this technique at all. In all probability this means that less than one per cent of American mothers will have this method for the next five years. This is a far distant objective from the "almost universal use of the method" promised to American women by the uncensored lay publicity.

In our experience we believe the contraindications to the method are the following:

1. Patients with easy, almost precipitate labors and patients who come into the hospital in the terminal part of the second stage of labor, less than forty minutes before delivery—for them a few whiffs of gas or ether, and, in the selected short cases, even ehloroform, are safer and more satisfactory than caudal analgesia. This group includes an estimated 10 per cent of hospital deliveries.
  2. Patients who are apprehensive, nervous, and desirous of being asleep when the baby is born and those who profess a fear of caudal analgesia because of the needle injection or because it is to them an "experimental" procedure, do not as a rule make good patients under this technique and should be excluded. They represent about 10 per cent of hospital obstetric patients.
  3. Gross deformities or disease of the spine or central nervous system, including syphilis of the central nervous system, tumors which narrow the spinal canal, abnormal extension of the sacral hiatus, abnormally low extension of the dural sac, history of epilepsy, hysteria, and emotionally unstable personalities preclude the use of this method. Trotter, on the basis of a study of several thousand sacra, estimated that more than 5 per cent have automic deformities in and around the sacral hiatus which would exclude successful use of the method. This group excludes another 10 per cent.
  4. Extremely obese individuals with large fat pads over the sacral hiatus preventing accurate palpation of the hiatus and adequate insertion of the caudal needle should not receive caudal analgesia. Approximately 3 per cent of patients can be listed in this group.
  5. Local infection (bacterial or fungus) at the site of the injection and patients with real, removed, and potential pilonidal cysts contribute to another 2 per cent of the contraindications.
  6. Profound anemia and dehydration, unless supplemented by oxygen inhalations and intravenous fluids.
  7. The obstetric complications can be grouped under one section:
    - a. Placenta previa unless used for immediate cesarean section.
    - b. Abruptio and incomplete or beginning premature separation of the placenta.
    - c. Patients with definite disproportions of pelvic and fetal diameters unless used for a trial of labor preliminary to a cesarean section.
    - d. Nulliparous patients with a floating and unengaged fetal head and patients with pendulous and weak abdominal walls in the presence of an unengaged fetal head.
    - e. In the birth of monstrous and predetermined dead babies.
- Approximately 5 per cent of hospital deliveries fall into this group.

8. History of sensitivity to the analgesic agent is an extremely rare but, indeed, definite contraindication.

Thus, we advise that these contraindications be observed rigidly by those beginning the use of caudal and continuous caudal analgesia.

The incidence of the successful use of this method can be increased if the hospitals and clinics anticipating its application would adopt a form of organization and teamwork between the obstetric and anesthetic staffs with an adequately trained nursing supplement.

First, the physicians using the technique should have a period of special training involving a study and correlation of anatomy, physiology, pharmacology, and the altered obstetrics produced with this method.

Second, the patient should be surrounded with safeguards of readily available oxygen, vasopressors, and sterile lumbar puncture needles for withdrawing the occasional inadvertent massive spinal injection that might result from carelessness for indicated cases.

Third, diligent attention should be given the supplementary diagnostic aids of the Bishop x-ray technique for minute study of the sacrum to rule out insurmountable anomalies. The results of the tocographic tracings now being performed in several hospitals should be watched for a study of uterine motility under caudal analgesia.

It should be emphasized that continuous caudal analgesia should not be continued indiscriminately. More than 80 per cent of the last one thousand cases managed in the Philadelphia Lying-in Hospital were given this form of pain relief for less than five hours per patient. It was designed to relieve the pains, not the early discomforts of labor. The incidence of failures and refractory pain rises sharply after eight hours of caudal analgesia.

The reported complications thus far encountered in 30,000 cases include 12 maternal deaths. Seven of these probably could have been avoided if the above criteria had been carried out. Three were definitely anesthetic deaths that related to a misuse of the principles and substituted principles. The small incidence of infection, the associated minor complications of drug reactions, postanalgesic aches and pains, and the incidence of failures approaching 10 to 20 per cent in even expert hands have been previously reported but should serve to emphasize that the method is not infallible and should be considered still in the developmental stage.

The originators of the method are still studying the many new problems associated with the technique and solicit the consultation of specialists in obstetrics and anesthesia in protecting the patient from the enthusiasts, the untrained, and the propagandist. With the obstetric collaboration of Doctors Vaux, Lull and the staff of the Philadelphia Lying-in Hospital, the labors and deliveries of more than 3,000 patients have been managed with this technique. We are convinced the method opens up a new horizon to the medical profession.

# Editorial

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## Again, Caudal Anesthesia

THE April, 1943, issue of this JOURNAL included an editorial on the subject of caudal anesthesia in obstetrics, in which attention was called to the rapidly spreading employment of this procedure, fathered as it was by extensive publicity both in lay and certain medical periodicals, and to the need of caution in its application. Contributions in great number have been added to the literature on the subject and thousands of cases reported with apparently favorable immediate results. Uniform standards of technique, however, have not been generally adopted and various authors have developed their own particular variations as to the choice of the anesthetic agent and the method of approach. In view of the general interest in the subject, we opened the pages of this JOURNAL for the publication of reliable and informative articles dealing with caudal anesthesia but found it necessary to exercise restraint in their acceptance unless they constituted definite additions to our knowledge of this procedure. What is still needed is the presentation of frank confessions of failures and complications. In no other way can a sound evaluation be made.

What may be regarded as a relief to the somewhat unrestrained endorsement of a captivating and dramatic procedure, is the admission by those who have had an extended experience and given careful thought to the matter, that this is not a measure for the relief of labor pains entirely free from risk, that it must be carried out by a specially trained personnel, that it is only to be employed in an adequately staffed and supervised hospital service with adequate cooperation between the anesthetist and the obstetrician. In other words, it is not to be accepted as a routine procedure nor as a salvation for mere pain relief. There are numerous "don'ts" to be observed, as shown in the recent article by Clifford Lull,\* and the "Stop, Look and Listen" sign displayed at unattended railway crossings still may be regarded as an effective if rather blunt danger signal by way of comparison.

Attention therefore is directed to the special article which appears on another page by Dr. Hingson, a proponent of the method and experienced in its use. We present it as a warning note in view of possible unfortunate developments if caution is disregarded in employing in what may prove in selected cases, a valuable addition to our obstetric armamentarium.

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\*Lull, C. B.: AM. J. OBST. & GYNEC. 47: 312, 1944.

Measures to alleviate the "pains" of labor have come and gone. One after another they were hailed as the *sine qua non* of proper delivery care but the continued search for new methods must be accepted as evidence that ultimate success is still to be achieved. It would be unwise and unjust to decry the efforts of those who desire to provide relief, when required, to women in labor but it seems equally unwise and unjust to prospective mothers to make them believe that each new procedure is generally applicable, or that it is absolutely safe for themselves or their babies. Thus there is still need for a more definite evaluation of caudal anesthesia, which cannot be regarded otherwise than as a major surgical procedure of equal importance with the obstetric conduct of the labor itself. The "don'ts" which must be taken into account by those who are tempted to resort to this method, and which have been stated so frankly by competent observers should receive commensurate publicity with the widely heralded advantages. We have by no means reached the goal.

# Correspondence

## Artificial Insemination

To the Editor:

It is commonly accepted in medicine that chronological precedence on this earth gives no one and no group any priorities flowing from a celestial O.P.A. or other heavenly agency. Medicine cannot recognize vested interests or rights even if it must, along with the rest of the community, appreciate terrestrial wealth and power. Scientific facts must be recognized from whatever source they come. We cannot degenerate to Nazi levels of thinking that anything we originate has a halo about it whereas anything that comes from the other fellow (not in our group or crowd) is false; is to be ignored and despised.

In 1941, we analyzed<sup>1</sup> the replies of several thousand physicians to the questionnaires sent by the National Research Foundation for the Eugenic Alleviation of Sterility, Inc., of Nesconset, L. I. Two years later a criticism of that analysis appeared.<sup>2</sup> We reviewed our material, including the printed article, the reprints thereof and the mimeographed sheets covering the findings which were distributed among physicians generally. We conclude without hesitation that we need offer no apology for what was written there except for the acts of our staff who failed to discover an erroneous statement of the totals of direct viable pregnancies. This should have been 3,523 boys (instead of 3,623) and 2,205 girls (instead of 2,105). However, the totals of these direct viable pregnancies, 5,728, and the grand total of all viable pregnancies, 9,238, were absolutely correct. We are glad to acknowledge further that an omission of 12 stillbirths was made although it was clearly stated in paragraph 2, of page 2 of the reprint that the number of surgical operations prevented (382) was 32 times as great as the number of stillbirths. A simple calculation would give the answer. We also wish to report that the mimeographed sheets mentioned that there were three sets of twins in the series. Through an oversight this was not included in the paper as it appeared in the *Journal of the A. M. A.*<sup>1</sup> We stated that 97 per cent of pregnancies gave living babies. By that statement we meant that the total of all viable pregnancies constituted 97 per cent of the grand total of all pregnancies; and so it was.

If any of these figures seemed too great or too small to the expert calculators who live in the realm of the slide rule, we have no explanation or apology to offer because the questionnaires reflected not the work of the authors but of the more than 7,000 doctors who replied.

Criticism was made on page 918 of the June article in this JOURNAL which demonstrates the failure to appreciate the difference between "pregnancies" and "viable pregnancies." That this should not seem clear to the physicist who was mysteriously drawn into the question as an expert is not surprising, but that a physician such as the reviewer, who adopted the conclusions of the physicist should not understand the difference is more than astonishing. It needs hardly be pointed out in these pages that all of those who become pregnant and give birth to live issue are termed viable pregnancies. Every woman who became pregnant was counted as a case of pregnancy initiated. When she became pregnant the second time, she was counted as a second case just as is done in clinics and in private records throughout the land.

<sup>1</sup>Artificial Insemination: Present Status in the United States as shown by a Recent Survey. Seymour and Koerner, J. A. M. A. 116: 2714, June 2, 1941.

<sup>2</sup>Status of Artificial Insemination, Clair E. Folsome, AM. J. OBST. & GYN. 45: 915, June, 1943.

Much was made of the insemination curve, and a tortured analysis led the reviewer to remark that there were less than 100 pregnancies in which 8 inseminations had been employed and that the next point on the graph showed 4,312 cases in which 12 inseminations were used. This was stated to demonstrate that there was 43 times as great a chance to become pregnant with 12 inseminations as with 4 to 8. Yet the critic admitted there were no reports for 4, 5, 6 or 7 inseminations.

However, the actual number of successes from 8 inseminations was reported by us as 61. The number for 12 inseminations (4,312) is therefore about 70 times (not 43 as stated by the reviewer) that for 8. This number (4,312) is about 10 times as great as reported for 3 inseminations but less than five times that reported for 9 inseminations. The reviewer chose to ignore entirely that there were almost 900 cases (897 to be exact) for 9 inseminations and proceeded to the number for 12. Perhaps this was accidentally omitted; certainly to include it would not seem to fit into the argument of his review.

Now, what do all these figures indicate as to incidence of successful insemination? No more and no less than the bare fact that successes occurred and were reported at these levels; certainly not the tortured misinterpretations and omissions of our critic.

By now it must be evident that our critic's own accuracy is not above review. And so it is. We are by no means finished with the flow of inaccuracy that came from his pen. He stated<sup>2</sup> on page 922 that our report showed that 2 out of every 3 doctors obtained parallel success. This statement does not coincide with what we wrote. We reported 7,642 replies of which 4,049 were successful. This is roughly a little more than one-half, and not two out of three.

In his reading matter the reviewer cited an article on sperm by Rubenstein as reference 61 while his bibliography listed that number for an article by Langman and Burr. We were interested in this reference and looked it up only to find that it was listed on the wrong page. When we finally found the article, we discovered it had nothing whatsoever to do with sperm but treated the subject of ovulation and its electrometric timing. To test the accuracy of the sarcastic comment cited as references 65 and 66, we took the trouble to look at these volumes. We found that 65 was a general article on "The Perpetuation of Error in Obstetrics and Gynecology" and apparently was referred to solely for the purpose of quoting the phrase "perpetuation of error." We submit this is everyday English and requires no bibliography unless it is the reviewer's purpose to add the weight of a name in medicine to an argument about which that person never wrote and about which the reviewer himself is not too sure.

Number 66 was even more illuminating, as it referred to a publication by K. Hyder which was cited as "Human Affairs 2: 37, 1941." Search for this in the library of the New York Academy of Medicine was entirely unproductive. We then went to the central branch of the New York Public Library at 42 Street where they searched through the Union lists and all other lists of which they had knowledge to determine whether this was a discontinued publication. No trace of it ever having existed could be found. So that no charge of incompleteness be levelled against us, we then inquired at the general library of Columbia University. They had no record of ever having heard of it. We concluded with a search at the library of the College of Physicians and Surgeons of that University with the same result. We simply list these inaccuracies to indicate that errors arise in spite of painstaking checking in the hands of even those who set themselves up as supervisors over the work of others. Charity forbids that we multiply the example.

Finally, we cannot overlook the editorial in the same issue of this JOURNAL.<sup>3</sup> The editorial writer stated that he wondered whether it is "desirable to lower the accepted human relationship in this respect (not in quote: substituting artificial

<sup>3</sup>Editorial: AM. J. OBST. & GYNEC. 45: 1066, June, 1943.



insemination for coitus) and in a sense to place them on a level with the propagation of animal life undertaken for convenience and gain." It is evident that such an opinion arises from a misconception of the facts. Artificial insemination is as much a modality for the treatment of sterility as the sulfa drugs are for infections. You would not think of refusing to employ the therapeutic marvels of the sulfa drugs just because we did not come supplied with them at birth? Shall we refuse to use insulin for the diabetic who needs it just because nature has failed to supply it in the patient's own tissues? Similarly, no one can refuse the last ray of hope remaining to the sterile—artificial insemination—in whom Nature has weakened or entirely cut off the ordinary source of his fertility.

The editorial further stated that the Christian and legal idea of marriage with its rites and responsibilities would likely be thrown into the discard through the employment of artificial insemination. On the contrary, neither of these systems of regulating human deportment are involved in artificial insemination as that is a method designed to perpetuate the marriage and allay the disrupting influences of infertility.

The commentator asked whether we can afford to overthrow the morality of the marriage state and approve the accompanying "unphysiologic" practices essential for this procedure (artificial insemination). The first part of this query has been answered above. A true appreciation of the procedure and the indications for artificial insemination will show the reader at once the error of the second argument.

In spite of all that has been learned about female physiology the secret of ovulation<sup>4</sup> has escaped us so far. Our ability to raise depressed or absent spermatogenic function is extremely limited. The married woman who is capable of impregnation but has a sterile mate very often is subject to a procreative urge which is irrepressible. How can she become with child other than through artificial insemination? What other choice has a woman who is infertile? Would those who argue against this method prefer polygamy, prostitution or adultery? To permit sterility to continue would be unphysiologic and would constitute race suicide. What the practitioner seeks to do by artificial insemination is to enable the physiologic processes of pregnancy to take place and save a worthy couple from the desolation of enforced barrenness or the disrupting influences of divorce.

53 EAST 96 STREET, NEW YORK CITY.

ALFRED KOERNER, M.D.

### Reply by Dr. Folsome

To the Editor:

Facts are stubborn things while hopes and figures are their aversion. Witness the "scientific" rebuttal, nine months delayed, of our medical confrere, Dr. Koerner, in the current issue of this JOURNAL, to our critical review on, "The Status of Artificial Insemination."<sup>1</sup>

It appears plain the principal proponents of that inquiring organization, *The National Research Foundation for the Eugenic Alleviation of Sterility, Inc.*, exhibiting one projected function in its unwieldy title, now claim to question the facts in our critical review. Their refutation is welcome. We heartily urge the reader to review the two articles under consideration.<sup>1,2</sup> In our opinion, the analytic remarks require no subtraction but rather one addition. Several months prior to the release of this critical review<sup>1</sup> of the Seymour and Koerner survey article,<sup>2</sup> the writer, in the company of a well-known gynecologist, Dr. Robert L. Dickinson, made a personal call upon Dr. Seymour for the express privilege of discussing the artificial insemination survey. As workers in the same scientific field, we asked many questions about correlations derived from their survey. As humble students manifesting

<sup>4</sup>Editorial: Detecting the Exact Time of Ovulation by Ovulation Potentials, J. A. M. A. 124: 298, 1944.

scientific curiosity, we asked Dr. Seymour about her documentary evidence hoping, as do most visiting fellow scientists, we would have the customary accorded privilege of reviewing her voluminous original source data. As the interview became prolonged, we openly requested this usually granted privilege. Our earnest efforts met a firm refusal from Dr. Seymour. It is this fact more than any other which prompted the critical analysis of the paper in question. The original data upon which it was based not being made available, is it little wonder that our scientific credulity was strained. The evidence as listed in the article under consideration was cloaked with a scant degree of objectivity as to methods and in arriving at such bold conclusions that a critical review was all the more clearly indicated.

Dr. Seymour revealed no information in the original article of the method employed, whether by intracervical or merely vaginal instillations of semen. What were the criteria, as used by those answering Dr. Seymour's survey, in the selection of cases assigned to the group using heterologous semen specimens? What scientific reasons were given by the answering physicians for the use of donor semen? Where are the time correlations as related to the time of insemination? These observations would have tremendously enhanced the value of the survey.

Is it little wonder we sought the aid of a skilled mathematician among others, who gave liberally of their time, to assist us in a critical evaluation of the article? as it was presented? It was solely from this fragmentary evidence that the mathematical data concerning the survey per se were obtained. *Our conclusions* based upon the only available numbers, submitted in publication by Seymour and Koerner themselves, *remain still unchanged*. We request the indulgence of the reader and ask that he or she again reread our analysis.

The writer admits two bibliographical errors, one of omission anent Rubenstein, and one of commission regarding the crediting of the omitted Rubenstein reference (*Federation Proceedings* vol. 1: No. 1, March, 1942) to Langman and Burr, an article which should have been listed independently. The original copy contained even more references. These were subsequently omitted in order to condense the review. The writer is indebted to Dr. Koerner for having these errata directed to his attention. Incidentally, the editorial "Canned Knowledge" in *Human Affairs* 2: 37, 1941, can be obtained from the files of the National Committee on Maternal Health, in the building of the New York Academy of Medicine.

It is unfortunate that Dr. Koerner has apparently missed the total purposes of our critical review on "the Status of Artificial Insemination."<sup>1</sup> We cannot endorse promiscuous heterologous artificial insemination. Upon indication, after careful study of each individual case, homologous artificial insemination may be advisable.

In the words of Guttmacher<sup>3</sup> which we emphatically reiterate, "*artificial insemination must never be an assembly line kind of medical treatment. . . .*"

In conclusion, the writer insists once again—"the principal reason for this critical review is to place on record a protest against publication of such *extreme claims* on the subject of human sterility until these are checked and verified." That conclusion stands for the reason stated by the writer in his original article<sup>1</sup> to which he invites the close scrutiny of interested readers.

A man protesting against incompatible fact is on the way toward uniting himself with all men that believe in truth. It is indeed a privilege to be in such complete accord with men like Guttmacher, Cary, Dickinson, Kosniak, et al. regarding heterologous artificial insemination.

PLAINFIELD, N. J.,  
MARCH 4, 1944.

CLAIR E. FOLSOME, M.D., F.A.C.S.

<sup>1</sup>Folsome, C. E.: *AM. J. OBST. & GYNEC.* 45: 915, June, 1943.

<sup>2</sup>Seymour, F. I. and Koerner, A.: *J. A. M. A.* 116: 2747, 1941.

<sup>3</sup>Guttmacher, A. F.: *J. A. M. A.* 120: 442, 1942.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Placenta

Wang, H. W., and Hellman, L. M.: Studies in the Metabolism of the Human Placenta: I. Oxygen Consumption in Relation to Ageing, *Bull. Johns Hopkins Hosp.* 73: 31, 1943.

1. The oxygen consumption of human placentas at different stages of pregnancy was studied.

2. The oxygen consumption of the human placenta decreases gradually as pregnancy advances, a fact in keeping with the changing histologic picture of the organ.

3. The oxygen consumption of the term human placenta is not influenced by the use of analgesics or anesthetics during labor.

4. Addition of glucose into the phosphate Ringer's solution does not increase the oxygen consumption of the human term placenta.

C. O. MALAND.

Blanco, J. T.: Placental Neoplasms, *Rev. de cir.* 14: 299, 1943.

Placental neoplasms are reviewed and discussed, with a case report, by the author. Placental neoplasms may be of either maternal or ovular origin. Those of maternal origin develop from the decidual cells and are of the conjunctival type, do not produce an increase of prolan, and are not necessarily the result of pregnancy. They are exceedingly rare and less malignant. Those of ovular origin arise in the epithelium, present a cellular polymorphism, characterized by anaplastic cells of Langhans, syncytium with monstrous deformities and at times with metaplasia of a decidual tendency and deformed decidual cells, of reactive significance and also with metaplastic tendencies that approximate morphologically those of the syncytium.

The diagnosis of these tumors is based on surgical exploration, histologic study and hormonal investigation. The prognosis is grave in the chorionepitheliomas, less serious for deciduomas, not serious in cases of benign mole and reserved in those of penetrating mole. The cases which are followed by spontaneous cure or after curettement are not true neoplasms, but simply retention of active placental rests or decidual endometritis. The only treatment is surgical removal, leaving radiation therapy for inoperable cases.

J. P. GREENHILL.

Jones, G. E. Seegar, Gey, G. O., and Gey, M. K.: Hormone Production by Placental Cells Maintained in Continuous Culture, *Bull. Johns Hopkins Hosp.* 72: 26, 1943.

It has been demonstrated that placental cells produce cyonin, that is, chorionic gonadotropin. The type of cells apparently responsible for this activity are the Langhans' cells. These cells will produce cyonin under conditions found in continuous tissue cultures and may retain this capacity as long as six months in culture. It has not been possible to demonstrate that placental cells can produce estrogen under similar circumstances.

C. O. MALAND.

## Pregnancy; Physiology, Diagnosis

Salles, A. de Aquino: *The Frank Eight Hour Test for Pregnancy*, Au. brasil. de ginec. 15: 467-476, 1943.

The author describes Robert Frank's eight-hour test for pregnancy which is based on the observation that chorionic gonadotropin produces a marked hyperemia of the ovaries in immature rats, detectable eight hours after the first injection. In 50 cases the results were so consistently satisfactory as to merit recommendation of this test which is simple, rapid and comparatively inexpensive.

J. P. GREENHILL.

Merchante, F. R.: *Contribution to Study of the Blood During Pregnancy*, *Semana méd.* 49: 1273, 1942.

Merchante studied the blood in 46 pregnant women. Hemoglobin was determined by the method of Wong, and cell volume by the method of Wintrobe. The red cell count also was determined. It was possible to follow eleven women from the first to the ninth month; the others were not followed regularly, through lack of interest or fear.

Results of the study show that the quantity of hemoglobin per cubic centimeter, the number of red cells per cubic millimeter and the cell volume are diminished from the beginning to the end of pregnancy. The level of hemoglobin shows a slight increase in the second month, but decreases abruptly in the third, and more slowly later, increasing in the eighth, and ascending slightly in the ninth month. The variation is from 12.55 grams per 100 cubic centimeters in the first month to 11.45 grams in the ninth, exceeding 13 grams in the second month.

The number of red cells per cubic millimeter decreases progressively from the beginning to the end of pregnancy, with at times a slight relative increase in the fourth month. The figures vary between 4,358,000 in the first month and 3,572,000 in the ninth. The cell volume descends progressively from 42.42 per cent in the first month to 38.96 per cent in the ninth, showing, in some instances, a slight increase in the second month.

J. P. GREENHILL.

Sloman, Lysbeth: *The Hippuric Acid Excretion Test in Pregnancy*, *M. J. Australia* 1: 293, 1943.

The author performed tests to establish figures for normal pregnancy and for complications of pregnancy without known liver disease. It was also determined how soon after parturition the hippuric acid excretion returns to normal. The figures for normal pregnancy indicate a progressive reduction in the excretion of hippuric acid as the pregnancy advances, while after parturition there is a statistically significant increase in the amount excreted, and the normal value for nonpregnant subjects is approached. The hippuric acid excretion rate for women up to three months pregnant is within the normal range for nonpregnant subjects, averaging 2.84 grams of benzoic acid. From 3 to 6 months there is a decrease in the excretion of hippuric acid (2.42 grams) and from 6 to 9 months there is still a further decrease (2.15 grams).

Of 22 patients with toxemia of pregnancy, the mean rate of excretion of benzoic acid was 1.96 grams. The author divides the toxemias into albuminuria, hypertension, hyperemesis, and pyelitis of pregnancy.

Tests were performed on 30 women whose hippuric acid excretion was tested before and after the baby was born. Results show that 18 of these patients reached or exceeded an excretion of 2,151 grams of benzoic acid on or about the eighth day of the puerperium. The majority of the patients suffering from

toxemia of pregnancy, however, failed to reach Quick's figure for normal excretion by about the tenth day of the puerperium. There is statistically a highly significant difference between the means of the tests carried out during the puerperium on toxemic patients and the tests carried out during the puerperium on normal patients. This was most marked in the pyelitis cases and in the opinion of the author was due to kidney dysfunction.

WILLIAM BERMAN.

### Radiation

Wasson, W. Walter: Intravaginal Roentgen Irradiation of Cancer of the Cervix, Radiology 40: 454, 1943.

The author describes another method of intravaginal roentgen irradiation of the cervix. The apparatus consists of a cylinder and proctoscopic light. The apparatus containing the x-ray tube may then be brought into contact with the cylinder and then clamped into position. This treatment is always combined with external roentgen irradiation of the pelvis. The cylinder may be angled to direct the rays against the cervix or into the broad ligaments or into any portion of the pelvis. By this method the rays are limited to an area conforming to the diameter of the cylinder. The author feels that with this method the results as to permanent cures will be no better in the early cases than those of radium and external roentgen therapy. There will be, however, less necrosis of the cervix, and likewise less infection of the vagina when this technique is employed. It is also felt that better results should be obtained in the advanced cases of cancer of the cervix than by any of the other methods which have been at the command of the radiologist.

WILLIAM BERMAN.

Kaplan, Ira: Irradiation of the Spleen and Pituitary for Control of Pubertal Bleeding, J. A. M. A. 121: 1199, 1943.

The author reviews the literature on the subject of irradiation of the spleen and the pituitary for intractable gynecologic bleeding. It is felt that the effect on the ovaries is an indirect one. In menorrhagia at puberty, or just beyond this period, roentgen therapy to the spleen and to the pituitary can be safely administered without interfering with subsequent ability to bear children. Even though in some instances radiation must be administered directly to the ovaries, seldom is sterilization in young women permanent, and whereas ova in the later stages of their differentiation are readily destroyed by irradiation the primordial cells which will produce subsequent ova are not affected.

The pituitary is definitely related to the productive organs, and has been shown to have a pronounced influence on menstrual function. This treatment of the spleen and the pituitary offers a readily available and effective method of treating pubertal bleeding without direct irradiation of the ovaries.

WILLIAM BERMAN.

### Vaginal Infections

Fuentes, C.: Preliminary Note on the Isolation and Identification of *Monilia albicans* in Cases of Vaginitis, With an Experimental Study, Rev. méd. cubana 53: 937, 1942.

The organism, *Monilia albicans* or *Mycotorula albicans* was studied by the author in experiments on 32 animals, including rabbits, white rats and Cuban rats. Renal and hepatic lesions were the principal result in animals in which the organism was injected into the veins. Attempts to produce experimental vaginitis in the animals studied, by local instillation, were unsuccessful.

Acetyl-amino-hydroxyphenylarsenic acid produced rapid disappearance of clinical symptoms. The author believes that this treatment has not been used previously in vaginitis due to *Monilia albicans*.

J. P. GREENHILL.

Taft, A. E.: Concerning the Nature of Intracellular Inclusions and Their Significance in Gynecology, *West. J. Surg.* 51: 342, 1943.

The relationship of intracellular and extracellular "inclusion bodies" to certain fungi and bacterial spores is discussed as pathogenic agents in the vagina. Inclusion bodies have been found in the squamous epithelium of the vagina following use of the vaginal tampon. It is suggested that protozoa, fungi and bacteria which are often present in the vagina as pathogens, may in their growth process pass through certain stages of which the inclusion body may represent one stage. An illustration is shown in which a protozoon appears as a lifeless granule in all respects similar to a virus or spore. Therefore, the inclusion body found in vaginal epithelium may illustrate just one part of the life cycle of pathogenic molds, bacteria or protozoa.

WILLIAM BICKERS.

### Venereal Diseases

Lewis, Robert M.: Management of Gonorrhea in the Female, *Am. J. Syph., Gonorr. & Ven. Dis.* 27: 418, 1943.

In the matter of diagnosis, laboratory evidence consisting of positive cultures or perfectly typical spreads is conclusive evidence of infection. Such evidence is usually obtainable with relative ease in acute cases. A small number of chronic cases yield positive laboratory evidence. Negative spreads and cultures, even if frequently repeated, must never be accepted as sure evidence that there is no gonococcal infection. While laboratory evidence is an essential part of diagnosis, in many instances history alone justifies a diagnosis of gonococcal infection and indicates immediate treatment.

Sulfanilamide, the first drug of real value in treating gonococcal infections, probably cured less than 30 per cent of the patients to whom it was given. Sulfapyridine proved very effective, but was found to be too toxic and, like sulfanilamide, has been discarded. Treatment with sulfathiazole is spectacularly successful in about 85 to 90 per cent of women with gonorrhea. Sulfadiazine is still under trial. Pregnancy does not contraindicate treatment. The only cases which might constitute an exception are those in which there is obvious kidney impairment.

Pelvic abscesses and those of the Bartholin glands still require drainage. The late results of gonorrheal salpingitis, adherent retroversions, etc., require surgical treatment.

There is no exact end point at which it can be said that cure has been effected. Medical judgment combined with negative bacteriologic evidence must be depended upon.

In the matter of gonorrheal vaginitis of children, it is now believed that in such cases the gonococcal infection is ordinarily limited to the vaginal mucosa and portio vaginalis of the cervix. Accurate diagnosis must depend on positive cultures. Sulfonamide therapy is the accepted treatment.

C. O. MALAND.

### Anesthesia, Analgesia

Diddle, Lieutenant A. W., M.C., U.S.N.R., and Hill, Lieutenant A. M., M.C., U.S.N.R.: Pulmonary Embolism During Continuous Caudal Anesthesia, *West. J. Surg.* 51: 427, 1943.

Maternal respiratory collapse, fetal distress, local infection, meningitis and other complications of continuous caudal anesthesia have been reported but this is

apparently the first case of fatal pulmonary embolism to appear. The patient was a healthy young woman, aged 22, who received adequate prenatal care including weekly antiluetic therapy for her syphilis which had been under treatment prior to this pregnancy. Labor was spontaneous at term and after 6½ hours of labor, a 15 gauge B-D spinal needle was inserted into the sacral hiatus and withdrawal of the plunger recovered no blood. A No. 4 ureteral catheter was passed through the needle to the third sacral vertebra and the needle withdrawn over the catheter. Forty c.c. of 1 per cent procaine were injected and prompt anesthesia extending to just below the umbilicus with relaxation of the anal sphincter promptly followed. Repeated injections were given about every 25 minutes and two doses of a sympathomimetic drug were given for a sharp drop in blood pressure. After 3 hours of anesthesia an attempt to deliver the baby by forceps from an R.O.T. position made it necessary to give a small amount of ether in order to apply the Kielland forceps. While under anesthesia the patient gasped once and ceased to breathe. She could not be revived and a stillborn fetus was delivered. At autopsy a large pulmonary infarct in the right upper lung lobe was found. Careful search of the brachial, femoral, uterine veins revealed no thrombi. Upon opening the sacral canal a soft blood clot was found and beneath it a thrombosed vessel. Complete pathologic study of the entire body failed to reveal any other possible source from which the pulmonary infarct could have come. Failure to obtain blood upon introduction of the needle is not conclusive evidence that the venous plexus has not been injured.

WILLIAM BICKERS.

Nicholls, A. B.: Analgesic and Anesthesia During Labor, *Obst. y ginec. Latino-Am.* 1: 426-430, 1943.

In 1938 the author began the use of intramuscular injections of sodium evipan for the relief of labor pains during the first stage. Recently he began the routine use of the drug intravenously during the second stage. As soon as the patient is asleep he delivers the baby with forceps. He believes sodium evipan does not interfere with uterine contractions but increases the period of expulsion. Hence the need for the use of forceps. In a series of 700 labor cases delivery was spontaneous in 207 and by means of forceps in 363. The anesthetics employed were evipan (162) chloroform (304) spinal (42) ether (16) Schleich's solution (3) emareon (2). No anesthetic was used in 83 cases.

J. P. GREENHILL.

### Cesarean Section

Stearns, Howard C.: Extraperitoneal Cesarean Section, *West. J. Surg.* 51: 468, 1943.

Evolution of the extraperitoneal cesarean section is briefly reviewed. To Waters goes credit for the operation employed by this author but he emphasizes that its principles were first laid down by Physick, von Ritgen, Thomas, Skene, Davis, and most important were the contributions of Latzko.

The transversalis fascia surrounds the abdominal cavity and where it enters the pelvis it becomes known as the fascia pelvica and fascia endopelvica. One lamina of the endopelvic fascia envelops the bladder and another the uterus. The important fact is that the peritoneal plica, both anterior and posterior, are firmly attached to this fascia and cannot be dissected from it by blunt dissection while the fascia laminae are relatively easy to dissect from both the bladder and the uterus. This point is the keystone of the extraperitoneal operation, for the dissection of the fascia from the posterior and left lateral wall of the bladder permits mobilization of the bladder away from the lower uterine segment and permits the elevation

of the uterine-vesical plica while it is still attached to the fascia, thus exposing the lower uterine segment. A series of drawings graphically illustrates the technique and anatomy.

The operation was done on 16 patients, 15 of whom were primiparas. All but three showed definite signs of infection and 3 potentially so. All were in labor, the shortest duration having been 24 hours and the longest 56 hours. All mothers recovered and two babies died, neither of the fetal deaths could be attributed to the operation. In 3 cases the bladder was inadvertently opened and in 7 the peritoneal cavity was opened accidentally, all were closed without difficulty. No case of peritonitis developed.

WILLIAM BICKERS.

De Rezende, J.: My Experiences With the Arciform Incision for Cesarean Section in Infected Cases, *Obst. y ginec. Latino-Am.* 1: 257-292, 1943.

The author is convinced of the superiority of the transperitoneal, cervical cesarean section and prefers the longitudinal arciform incision to the straight vertical or horizontal ones because it is parallel with the muscle fibers. He is of the opinion that the extraperitoneal operation causes useless and even injurious complications resulting in prolonged intervention, delay in delivery of the fetus, accidental opening of the peritoneal cavity in 50 per cent of the cases, cellulitis and other complications. Since 1936, the author has performed 66 cesarean sections using a modified Kerr technique. There were two maternal deaths in this series but 64 women were contaminated at the time of operation, that is they had fever and tachycardia and they had had numerous vaginal examinations. He uses ether now but formerly employed spinal anesthesia. He gave up spinal because of its risk. Among 10 patients treated locally with sulfanilamide, 8 presented serious symptoms of intolerance.

J. P. GREENHILL.

## Gynecology

McKim, G. F., Smith, P. G., and Rush, T. W.: Dysuria and Nocturia in the Presence of Normal Urine in the Female, *J. A. M. A.* 123: 603, 1943.

The authors quote numerous causes of bladder complaints without pyuria, and stress the importance of careful and complete examination of the patient as a whole, and not just the urinary organs. The question of gynecologic disorders with bladder symptoms is of extreme importance. Great stress is laid upon the psychologic approach to the patient's symptoms, since many of these cases show functional bladder complaints which, to the patient, are quite real. Many times the symptoms due to the functional derangement are much greater than the pathologic picture would indicate. Such minor alterations as changing the brand of the patients cigarettes, their diet, or their cough medicine often bring about remarkable changes in the patient's symptoms. Some of the office procedures used in examining these patients and treating them are described.

WILLIAM BERMAN.

Araya, R.: Fundamental Conceptions of Ovarian Histophysiology, *Obst. y ginec. Latino-Am.* 1: 293-316, 1943.

The author maintains that in accordance with previous studies he believes (1) there is no chronologic relationship between ovulation and menstruation, (2) there is no correlation between the development of the Graafian follicle and the corpus luteum and the changes in the endometrium, (3) the endometrial changes are brought about by estrogen and progesterone. The author maintains that the Graafian follicle and the corpus luteum have no great influence in the production of the ovarian hormones.



The author studied 50 extirpated ovaries and found absolute predominance of all forms of atretic follicles over the few fresh follicles and corpora lutea. He found lipids in the ovarian stroma in all stages of development of the atretic follicles and at all times in the cycle and maintains that this is evidence of the continuity of ovarian secretion and coordination with several other ovarian constituents.

J. P. GREENHILL.

Machado, L. M., and Junqueira, M. A.: *Angiomatosis of the Cervix*, *Obst. y ginec. Latino-Am.* 1: 348-355, 1943.

The authors describe two cases of a new gynecologic pathologic condition which consists of diffuse angiomatosis developing along the fibromuscular connective tissue submucous layer of the portio vaginalis. The etiology is considered to be chronic cervicitis. Typically the cervix is spongy, very tender, enlarged and violet colored. Histologically, the tissue resembles a hemangioma. The predominating symptom is metrorrhagia following coitus or any trauma. The exact diagnosis can only be made by biopsy. The treatment consists of amputation of the cervix. The prognosis is good.

J. P. GREENHILL.

Lima, B.: *Colpectomy for Genital Prolapse*, *Obst. y ginec. Latino-Am.* 1: 452-465, 1943.

According to the author colpectomy is the most efficient way to treat genital prolapse. In old women the operation competes with vaginal hysterectomy. Partial colpectomy is easy to perform under local infiltration anesthesia, and total colpectomy may be indicated in cases of prolapse following hysterectomy. The results of colpectomy are excellent and the mortality and morbidity are low.

J. P. GREENHILL.

## Labor, Management, Complications

Hennessy, James P.: *Occipitoposterior Position*, *J. A. M. A.* 123: 524, 1943.

The many theories of the cause of occipitoposterior presentation are referred to. The author's experience has shown that the narrower the anterior pelvis, the higher the percentage of posterior positions. The etiologic importance of deflection of the head depends a great deal on such pelvic asymmetry as disturbs the equality of pressure on the ends of the occipitosincipital lever. Weak labor pains are also a factor. Flabby abdominal muscles are also important. Posterior positions are likely to be a cause of difficult labor, owing to the fact that the head is usually extended when the difficulty is encountered. On an average it lasts from 2 to 4 hours longer in a primipara, and from one to two hours longer in a multipara. In the majority of cases rotation occurs spontaneously, but the majority of obstetricians have tried to correct this abnormality and thereby shorten the second stage of labor and spare their patients. The prominence of the ischial spines is of greatest importance in determining whether intervention is necessary.

The author prefers not to give the patient any sedation until the cervix is dilated to 3 or 3.5 cm. Operative interference depends upon whether or not the head is engaged. If the head is at the spines  $1\frac{1}{2}$  to 2 hours is allowed for rotation; if it is below the spines about one hour is allowed. When manual rotation is used the author uses Schumann's modification of Pomeroy's technique, and if forceps are used the author prefers Bill's modification of the Scanzoni maneuver. The author uses the Kielland forceps infrequently. Cesarean section was used in 17 cases but the occipitoposterior position was not the sole indication.

WILLIAM BERMAN.

Guiroy, A. J., and Albertelli, J. F.: Regulation and Management of Delivery, *Bol. soc. de obst. y ginec. de Buenos Aires* 22: 23-45, 1943.

On the basis of a preliminary experience, from 1933 to 1937, with 866 cases, the authors describe the routine use of pituitrin administered intravenously in cesarean deliveries and dystocia, and in patients who have difficulty in expelling the placenta because of an atonic uterus. In the years 1938 to 1941, the proportion of patients treated with oxytocics varied from 4.75 to 5.71 per cent of the total number of deliveries. A very small number of these had spontaneous deliveries, a larger group (approximately one-third) had cesarean births, and the remainder required obstetric intervention.

The authors stress the following points in regard to the technique. The product used must be pure and must be diluted in a solution which allows administration of the exact quantity required and in a correct length of time. The effective dose is 2 to 5 units. The hormone preparation must be injected slowly. It should be used promptly, preferably immediately after the cord is severed.

The value of the procedure is proved by intact placentas and membranes, no untoward general reactions and retraction of the uterus with a minimal loss of blood. Frequently when the cervix must be repaired, prolapse of the lower uterine segment is observed, and thorough investigation must be carried out to avoid this in suturing the cervix.

The authors have employed pituitrin in the acceleration of delivery in hydramnios, twin births, uterine fibroids, inertia during the expulsive period and in a great number of other obstetric circumstances.

J. P. GREENHILL.

### Newborn

Sakula, J.: An Outbreak of Gastroenteritis in the Newborn Infant, *Lancet* 245: 758, 1943.

Epidemic gastroenteritis in the newborn infant often carries a mortality of 80 to 90 per cent. In the central Middlesex County Hospital on Nov. 1, 1942, it was observed that 2 out of the 6 babies in the premature nursery had a gastroenteritis and they were sent to the children's ward in the main hospital. Within a few days more cases appeared both in the nursery and in the ward to which the infected babies had been sent. On the fourth day after onset of the epidemic, the first mortality occurred. Healthy children were immediately isolated as well as the ill ones. Of the 31 children who were in the hospital, 18 became infected and 15 died, a case mortality of 83 per cent. The course of the disease was typical, beginning suddenly with severe and protracted vomiting, weight loss, normal or only slight elevation of temperature, and within a day or two these symptoms were followed by a persistent diarrhea. The stool often had an orange color. Treatment was apparently of no value. Saline with glucose was helpful in maintaining hydration. The sulfonamides were found to be without effect.

Autopsies were performed on 13 of the patients. Conspicuous was the absence of intestinal pathology. Most striking was the marked vascular congestion of the liver, thymus, and adrenals. The author believes the disease is probably not primarily an intestinal one at all, rather it is a generalized toxic condition. Culture of the feces revealed no consistent bacteriologic findings.

Suggestions are made as to how to prevent and how to stop (when already established) these outbreaks of gastroenteritis. Most important is the feeding problem. In this outbreak all cases occurred in babies who were either entirely or partly bottle fed. Completely breast-fed babies did not become infected. It is apparent then that infection occurs by way of the formula. A nurse should be appointed for the preparation of infant feedings whose sole duty it is to prepare and serve those formulas. Cross infection from other babies is thus avoided.

WILLIAM BICKERS.

Page, Earnest W.: *The Excretion Rates of Histidine in Pregnant and Nonpregnant Women*, West. J. Surg. 51: 482, 1943.

Histidine is an essential amino acid making up about 2 per cent of most proteins in the human body. Since Voge first suggested that it was excreted in large amounts in pregnancy and Kapeller-Adler suggested a method of qualitative analysis that made it a practical laboratory procedure, much interest has been elicited. Published opinions as to its specificity in the diagnosis of pregnancy are at wide variance. The author has shown that random specimens of urine from the same patient show wide variations in histidine content. Using a method analysis which is described in detail, it was found that the variations were so great that no conclusions could be drawn when urine specimens were taken at random. Consequently it was decided to study the histidine excretion rate of the patients at various stages of pregnancy and the normal and toxemic patient, also the nonpregnant individual. Quantitative analysis for histidine by the author's method before and after the ingestion of 1 gram of this amino acid was done on these patients. The highest excretion occurs between the third and eighth month of gestation, the rate falls during the 2 weeks before delivery. Excretion rate is much higher in the pregnant than in the nonpregnant woman.

WILLIAM BICKERS.

Swan, Charles, Tostevin, A. L., Moore, Brian, Mayo, Helen, and Black, G. H. Barham: *Congenital Defects in Infants Following Infectious Diseases During Pregnancy*, M. J. Australia 2: 20, 1943.

The authors report the results of 61 infants examined, 36 having been found to have congenital defects. The mothers of 49 infants had suffered during pregnancy from rubella, 4 had no knowledge of any exanthem during this time, 9 contracted morbilli during pregnancy, and 2 suffered from mumps. In the cases of rubella during pregnancy, 31 of the infants born subsequently exhibited congenital defects. The abnormalities included cataract, deaf mutism, heart disease, microcephaly, and mental retardation. With few exceptions all of the 31 mothers with congenitally defective children had contracted rubella within the first three months of pregnancy. Four cases of congenital cataract are described, in some instances associated with other defects. The mothers, in these cases, denied all knowledge of an exanthem during pregnancy. No congenitally defective babies were born subsequent to the occurrence of morbilli in pregnancy. One case is recorded of congenital corneal opacity following mumps during pregnancy. The operative procedure and postoperative follow-up are described.

WILLIAM BERMAN.

Calvo, J. A.: *Concerning the Congenital Pigmented Spot or Mongolian Spot in Colombia*, Obst. y ginec. Latino-Am. 1: 317-323, 1943.

The "congenital pigmented spot" also known as the "Mongolian Spot" or "blue sacral spot" is observed frequently among babies born to those with pure African blood or a mixture of it in Colombia. The spot is evident on the first day of birth and is almost a constant finding in the yellow and Mongol races. The spot is pyriform in shape and its lower border corresponds to the intergluteal furrow. Its color varies from green to gray-blue and its size is that of an adult's hand or even larger. Occasionally it is aberrant for it has been observed on the shoulders, back, neck and even on the limbs. Histologically, it is produced by special pigments deposited in the deep dermal cells called the Boelz cells.

The Mongolian spot has been regarded as an atavistic sign remaining from the Asiatic origin of the human race.

Among 350 babies born in the Bogotá Maternity, twenty-four had the characteristic "Mongolian spot" an incidence of 7 per cent. Among the remaining children without spots, 50 per cent had been born of a European mother or father and a Colombian white-skinned male.

J. P. GREENHILL.

### Pregnancy, Physiology

Schaffer, B., and Ricci, Guido: Influence of Age on Primiparity: A Study of 1,688 Cases, *Bol. soc. de obst. y ginec. de Buenos Aires* 22: 47-66, 1943.

Difficulties and complications attending a first pregnancy and childbirth have generally been considered to increase with the age of the mother, and 18 to 23 has been accepted as the optimal time for bearing a first child. The unfavorable factors in older women are largely due to loss of elasticity of the birth canal and deficiency in motor function of the uterus. But great differences exist in individuals, due to constitutional, gynecologic, social and even racial factors.

In a series of 3,835 obstetrical cases at the Maternidad Martin, 44 per cent, or 1,688 were primiparas. Of the primiparas, 25 per cent were less than 20 years, 43 per cent were between 20 and 25, 23 per cent were between 25 and 30, 7 per cent were between 30 and 35, and 3 per cent were more than 35.

Toxic conditions of pregnancy were most frequent in mothers between 30 and 35 years. Above 35, there was a marked decrease in these manifestations. The explanation advanced by the authors for this fact, which is contrary to most previously published statements, is that the older primiparas, as a group, were from a higher cultural level and were aware of the dangers of pregnancy at their age, and hence had better prenatal care.

In the group from 30 to 35, 5 per cent had breech presentations; in those more than 35, this percentage was increased to 11 per cent. In the oldest group, there were also 2 per cent transverse presentations. It is suggested that perhaps the decreased elasticity of the uterine musculature and abdominal pressure might account for these abnormal presentations.

Premature rupture of the membranes occurred with a frequency directly related to the age of the primiparas. The duration of labor also increased with age. In the group aged 30 to 35, 14 per cent had labors of 15 to 20 hours; 11 per cent 20 to 25 hours; 10 per cent, 25 to 30 hours; 2 per cent, 30 to 35 hours; and 10 per cent, more than 35 hours. In those over 35, 13 per cent had labors lasting more than 35 hours.

The mortality for the entire group of primiparas was 0.35 per cent. In those 30 to 35 years of age, it was 1.72 per cent; there were no deaths among the primiparas more than 35 years. Fetal mortality was practically uniform among mothers under 30, increased sharply among the older primiparas. Nevertheless, most of the fetal deaths were not due to prolonged or difficult labors, but resulted from prematurity and fetal maceration.

J. P. GREENHILL.

Leon, J.: Cystic Corpus Luteum and Lutean Cysts of the Ovary in an Apparently Normal Pregnancy, *Bol. soc. de obst. y ginec. de Buenos Aires* 22: 99-122, 1943.

The author reports the case of a woman, aged 33, a para iii, who had had amenorrhea for a few weeks, and complained of pain in the lower quadrant, nausea and vomiting. Vaginal examination revealed a slight increase in the size of the uterus and an adnexal cystic tumor. The Friedman reaction was positive. The diagnosis of early pregnancy with appendicitis and an ovarian cyst was considered as well as that of a persistent corpus luteum because the latter is characterized

by an enlarged ovary, amenorrhea and an increase of gonadotropic hormones. Operation revealed only slight inflammation of the appendix, but marked change in one ovary.

The corpus luteum in the removed ovary presented macroscopically the structure of the corpus luteum of gestation, that is, of an intrauterine gestation, but there was also no doubt that the gland displayed abnormalities similar to those seen in patients with ectopic pregnancy in which the embryo has succumbed. The corpus luteum was large (30 by 20 mm.), several millimeters larger than that generally observed in a physiologic pregnancy. Recently, numerous studies have shown that the size of the corpus luteum is greatest during the first months of gestation. Section of the corpus luteum showed that its wall of yellowish color, was 2 to 4 mm. wide, and the remainder was a cavity containing fluid. Histologic study of the wall of the corpus luteum showed the typical yellow cells which persist throughout pregnancy, some more obscure than others, probably representing different phases of secretory activity, as occurs in other glands of internal secretion; there also might be the possibility that the more definitely colored cells were filled with calcium salts, since this calcification is characteristic in gestation. Microscopic examination also revealed numerous thecal cells, which arise from the internal theca and play their greatest role in the second to third month, occupying the periphery or the corpus luteum, in intimate contact with the elements of the theca externa and the blood vessels.

The ovary also contained a number of lutean cysts of variable size, with gelatinous contents. It is unusual to encounter a number of these cystic formations in an apparently normal pregnancy.

Quantitative investigation seven days after operation revealed a definite hyperprolauria (more than 16,000 Brindeau units per liter of urine). The author admits that the concentration of prolaur may have been increased after removal of the corpus luteum, but cites experiments which showed that progesterone inhibits gonadotropic activity. The evidence of increased secretion of prolaur was the only abnormal finding in this patient. The pregnancy proceeded to term, and reports received from the patient, who had moved away indicated that gestation and delivery were entirely normal.

J. P. GREENHILL.

### Pregnancy, Complications

**Braze, Major Alexander: Bicornate Uterus With Pregnancy in Each Horn, J. A. M. A. 123: 474, 1943.**

The author presents the embryologic aspects of bicornate uterus and quotes the reports of the same in the literature. Stress is laid on the complications chief. of which, are hemorrhage and incarceration of one of the horns during labor. He reports a case of a pregnancy in each horn which delivered spontaneously only to be followed in three months by a prolapse of the left horn of the uterus with incarceration. A laparotomy was done which substantiated this diagnosis and a hysterectomy was carried out. The patient recovered.

WILLIAM BERMAN.

**Lavarello, A.: Diabetic Coma in Pregnancy, Bol. soc. de obst. y ginec. de Buenos Aires 22: 71-75, 1943.**

The author reports a fatality in a patient who had not been recognized as diabetic previously. A few days before the onset of the coma, she was abnormally thirsty, later she had severe vomiting, and then lapsed into coma, but was not brought to the hospital until 19 hours later.

In discussing the problem of diabetes and pregnancy, the author remarks that it is possible and appears probable that regulation of diabetes from the beginning

to the end of pregnancy can prevent all complications both to the mother and child. Not only should the diabetes be well controlled, but care should be taken that the metabolism of hydrocarbons takes place normally every hour of the day and night. In this connection, protamine-zinc-insulin is of great value.

During pregnancy, especially during the second and third trimesters, sudden and definite variations in the severity of the diabetes may occur; these may require more or less insulin. If the situation is not controlled promptly, it may result in serious consequences to both mother and child. As a rule, during the second and third trimesters of pregnancy, the diabetic patient should be examined every week or ten days. During parturition, the most rigorous care should be exerted to prevent acidosis and hypoglycemia in the mother. All authors agree that acidosis is a very serious complication and its fulminating progress can result in grave consequences. Occurrence of dangerous hypoglycemia in the newborn infant apparently can be prevented by maintaining the insulin intake of the mother within reasonable limits, and controlling the insulin dosage with frequent blood sugar determinations.

Routine cesarean section in diabetic patients is unnecessary and this procedure should be resorted to only when the obstetric indications for it are the same as in a nondiabetic mother.

J. P. GREENHILL.

Lastra, E. T., Jakob, A., and Sang, H. W.: *Placenta Accreta and Placenta Previa*, *Obst. y ginec. Latino-Am.* 1: 324-347, 1943.

One of the greatest dangers to the parturient woman which still exists in spite of progress in obstetrics is hemorrhage and its consequence, shock. Placenta accreta is one of the rare causes of hemorrhage and shock. The authors observed two cases of this complication. In the first case the membranes ruptured at the sixth month and because of failure of dilatation of the cervix in spite of good pains, a vaginal cesarean section was done. Hemorrhage followed retention of the placenta. Attempts to remove the placenta proved futile because of abnormal adherence. A diagnosis of placenta accreta was made and a supravaginal hysterectomy was performed. This woman had previously had a curettement 12 days after labor.

The second case reported was one of placenta previa treated by cesarean section. A curettement had likewise previously been done in the puerperium because of hemorrhage in puerperium. The placenta could not be removed so the uterus was amputated.

J. P. GREENHILL.

Lascano, J. C., and Valenzuela, J. R.: *Concerning the Medical Treatment of Eclampsia*, *Obst. y ginec. Latino-Am.* 1: 399-412, 1943.

During the last three years, the maternal death rate among the cases of eclampsia in the Cordoba Maternity was 6.7 per cent and the fetal death rate was 40.7 per cent. Strict medical therapy was carried out in 64.4 per cent of the cases. Among the sedatives employed were morphine, luminal and magnesium sulfate either alone or combined with intravenous hypertonic glucose solution and subcutaneous insulin. The authors believe that it is better to use a combination of luminal and chloral in women who have convulsions in pregnancy and a combination of luminal and magnesium sulfate when the convulsions occur during labor.

J. P. GREENHILL.

# Society Transaction

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## THE OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF JANUARY 12, 1944*

The following program was presented:

**How a Child-Caring Agency Places for Adoption.** Miss Beatrice MacNally, Adoption Supervisor of the Children's Bureau of Philadelphia (by invitation).

**Legal Pitfalls in Child Adoption.** Mrs. Lillian L. Strauss, Attorney (by invitation).

**Post-Partum Sterilization: A Generally Indefensible Procedure.** Edward A. Schumann, M.D.

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## Original Communications

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### OVARIAN FIBROMAS: A CLINICAL AND PATHOLOGIC STUDY OF TWO HUNDRED AND EIGHTY-THREE CASES

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*(From the Section on Surgical Pathology and the Division of Surgery,  
Mayo Clinic)*

EXACTLY two hundred years have elapsed since Astruc<sup>1</sup> in 1743 gave to the medical literature the first description of an ovarian fibroma. He emphasized the rarity of this type of tumor. For the next hundred and forty years isolated articles on the subject dealt mainly with certain gross pathologic changes which were seemingly peculiar to this neoplasm, to whose clinical manifestations very little attention was directed. In 1882, Coe<sup>2</sup> in an excellent review studied the histogenesis of ovarian fibromas, deciding that they represented an overgrowth of the ovarian stroma. He observed the frequent occurrence of edema in the tumor substance and correlated its presence with the formation of "geodes" or degenerative cysts. Twenty years later, in 1902, Peterson<sup>13</sup> in a succinct review first correlated clinical and pathologic data from reports of a total of eighty-two cases found in the literature and from a careful study of two cases of his own. He remarked on the slow clinical evolution of these tumors, and, pathologically, the relative absence of adhesions with a notable incidence of ascites. Peterson's investigations stimulated interest on the part of others and from 1902 to 1920 fibromas "came into their own," so to speak.<sup>5</sup> Accordingly it became apparent that (1) ovarian fibromas were not in fact pathologic curiosities; (2) they were by no means clinically silent.

Another spark of enthusiasm was touched off by Meigs and Cass.<sup>11</sup> These investigators pointed out that ovarian fibromas, although essentially benign in their evolution, sometimes produce clinical hydrothorax in addition to ascites. "Meigs' syndrome"<sup>2, 9</sup> now embodies the

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clinical triad of ovarian fibroma, ascites and hydrothorax—a combination which in the past had been interpreted all too frequently in terms of “inoperable malignancy.”

Finally, no review, however brief, would be complete without reference to the theca-cell tumor described in 1932 by Löffler and Priesel.<sup>10</sup> These investigators discovered that certain “fatty fibromas” were associated notoriously with periodic postmenopausal bleeding. The separation of the members of this “functioning” or theca-cell class from the general group of fibromas wrote a new chapter in gynecologic pathology. From our standpoint, it was felt that a clinical and pathologic analysis of a relatively large group of patients who had ovarian fibromas might throw some light on the incidence, histogenesis, complications and so forth, of this much neglected type of tumor.



Fig. 1.—A small fibroma is seen springing from the ovarian cortex.

### Materials and Methods

Records from the Division of Surgical Pathology and the section on pathologic anatomy of the Mayo Clinic were examined carefully for tumors bearing the designation fibroma, fibromyoma, fibroblastoma, xanthofibroma and so forth, affecting the ovary. Approximately 350 tumors included under these headings had been found at surgical exploration or at necropsy on patients seen at the clinic from 1907 to 1942, inclusive. Pathologic material was next secured and the tumors were studied in gross detail for data pertinent as to side, size, color, consistency, degree of encapsulation, edema, formation of cysts, and so forth. Associated pathologic lesions of the uterus and Fallopian tubes were recorded when these tissues were present. These data were all recorded carefully on specially prepared cards. Multiple blocks were then cut from the tumors and attempts were made to select regions which included also (in the same block) material from any identifiable ovarian substance. These blocks were placed in a fresh 10 per cent solution of commercial formalin, cut at a thickness of 10 microns on a freezing microtome, and stained routinely with hematoxylin and eosin. When

indicated, special stains such as the Galantha stain for mucin, sudan III stain, and the van Gieson stain for hyaline substance were also employed. Several thousand sections were thus made available for study. Preliminary microscopic "scouting" eliminated the occasional examples of granulosa tumor, theca-cell tumor, Krukenberg tumor and Brenner tumor from the series. A fair number of adenofibromas was found and similarly deleted. Three hundred and twelve "residual" ovarian fibromas (Fig. 1), occurring in a group of 283 patients, constitute the basis of this report.\*

### Clinical Features

*Incidence.*—The incidence of fibromas was ascertained to be slightly more than 5 per cent of all surgically removed ovarian tumors. Because the comparison did not include cases of inoperable pelvic malignant lesions of undoubted ovarian origin this figure of 5 per cent is somewhat higher than that which actually exists. Rhodenburg<sup>14</sup> found the incidence of ovarian fibromas to be 5 per cent; Hellman<sup>7</sup> expressed the opinion that an incidence of 2 per cent is more nearly correct.

*Age of Patients.*—The average age of patients who had ovarian fibromas was forty-eight years; the age of the youngest was sixteen and of the oldest was seventy-nine years, respectively. No patients were in the first decade, the second accounted for two, the third decade for nineteen, the fourth for fifty-one and the fifth for seventy-five. The sixth decade led the list with eighty-eight patients while forty-two patients were in the seventh and six in the eighth decades, respectively. Thus 31 per cent of the patients were from fifty to fifty-nine years of age, inclusive—an incidence for the sixth decade which agreed well with the figure of 28 per cent cited by Peterson<sup>13</sup> in his review. Our failure to find ovarian fibromas in the prepubertal age group of patients paralleled the observations of others and perhaps lent some support to the hypothesis of origin conceived by Brothers,<sup>3</sup> namely, that the hemorrhage attendant upon ovulation might be a significant "inciting agent" in the development of these tumors.

*Marriage and Pregnancy.*—Forty-three of the patients were single, 233 were married and in seven cases the civil state was not mentioned on the record. Of the married patients 185 had given birth to one or more children for a total of 503. Forty-three of the patients had been described as "childless" and in five cases information on this family item was not available. Accordingly, in the present series, as with others reported in the literature, evidence was lacking that the development of fibroma influenced the parity of the patient or was influenced by it. On the other hand, it should be recalled that the majority of fibromas became clinically manifest after the climacterium.

*Complaints.*—The commonest presenting complaint was the presence of a tumor. Eighty-eight patients had noted this symptom for an average period of thirty-three months with extremes of one week and thirty years marking the "time limits." The tumors were described generally as being of slow growth but a few of the patients had observed episodic increases of the size of their abdominal masses. Frequently these episodes were associated with the development of pelvic pain. However, forty-five patients in this group described the evolution of their tumors as being painless and in the remainder pain was frequently not very severe. Twelve patients had noted that the mass shifted with certain

\*Fifty-five of these tumors were reported previously by Hoon.<sup>3</sup>

shifts of body position. (However, this phenomenon has been observed also among patients who have ovarian cysts and uterine fibromyomas).

Pain was the principal complaint listed in the records of seventy-nine patients. In general, it did not have any diagnostic features. In thirty-six cases, it was present as the sole complaint, and in forty-three, it was noted in association with a tumor mass. In twenty-one cases the pain was more or less dragging, was located in the lower portion of the abdomen or in the flanks, and usually was without extension. In fifty-eight instances it was sharp, coming on in attacks. In no less than forty-nine of this latter group of cases, there was ascites or adhesions or both plus a noteworthy incidence of an edematous, twisted tumor pedicle. The latter was adjudged accordingly as an important etiologic factor in the production of pain.

Symptoms referable to interference with urinary function (frequency, nocturia and dysuria) occurred either alone or in combination with other symptoms in forty cases in this series. These urinary difficulties appeared to be related to ovarian fibromas of an average large size but did not differ otherwise from the similar disturbances noted among patients who had ovarian cysts. Their basis appeared to be mechanical compression of the urinary bladder. Backache, "pelvic pressure," "piles" and "varicose veins" were included in a long list of incidental symptoms with a similar etiologic basis. In 138 of the records, the listed symptoms were ascertained to have had no relation to the presence of the ovarian fibroma (usually small). They were produced by the "associated pathologic lesions" described elsewhere in this paper. These symptoms included "irregularity of menstrual flow," which in our analysis rarely could be attributed to the presence of an ovarian fibroid. The discovery of seven theca-cell tumors in our original group easily explained the phenomenon of periodic postmenopausal bleeding associated with certain atypical tumors.

*Physical Findings.*—Although the clinical diagnosis of "fibroid" was made in fifty instances, in only a few was the designation "ovarian" appended. In the case of larger neoplasms the notations "ovarian tumor with ascites," "ovarian cyst," "movable pelvic-abdominal tumor" and so forth appeared. In twenty-five instances a twist of the tumor pedicle was believed to exist. In twenty instances the presence of abdominal ascites was demonstrated and fairly frequently resulted in the notation "malignant." In two of these cases concomitant hydrothorax was apparent. With many of the symptomless fibromas the conditions indexed referred to the "associated pathologic lesions."

Laboratory data did not contribute any pertinent diagnostic information. Roentgenographic studies, including the occasionally indicated simple roentgenogram, although frequently demonstrating the presence of a soft-tissue shadow in the pelvis, rarely led to the identification of the type of tumor.

In summarizing the foregoing data we might say briefly: Small ovarian fibromas (those less than 4 cm. in diameter) rarely produce clinical symptoms. Large ovarian fibromas duplicate the clinical picture of any slowly growing pelvic tumor plus an unusually high incidence of ascites. A moderate degree of mobility and a firm consistency of fibromas predispose to twisting of the pedicle of the tumor with consequent pain. In the absence of infallible clinical signs, the diagnostic issue must be settled by surgical exploration of the pelvis. To decide otherwise denies the benefit of cure to many patients in whom

the presence of ascites suggests the existence of an inoperable malignant process.

The treatment of fibromas of the ovary is always surgical and no matter how small a solid tumor of the ovary is when first recognized, removal should be advised, as the possibility of a malignant lesion must always be considered and can be ruled out only by examination of the growth. The other ovary should always be examined carefully, as the possibility of other smaller, similar tumors must always be considered.

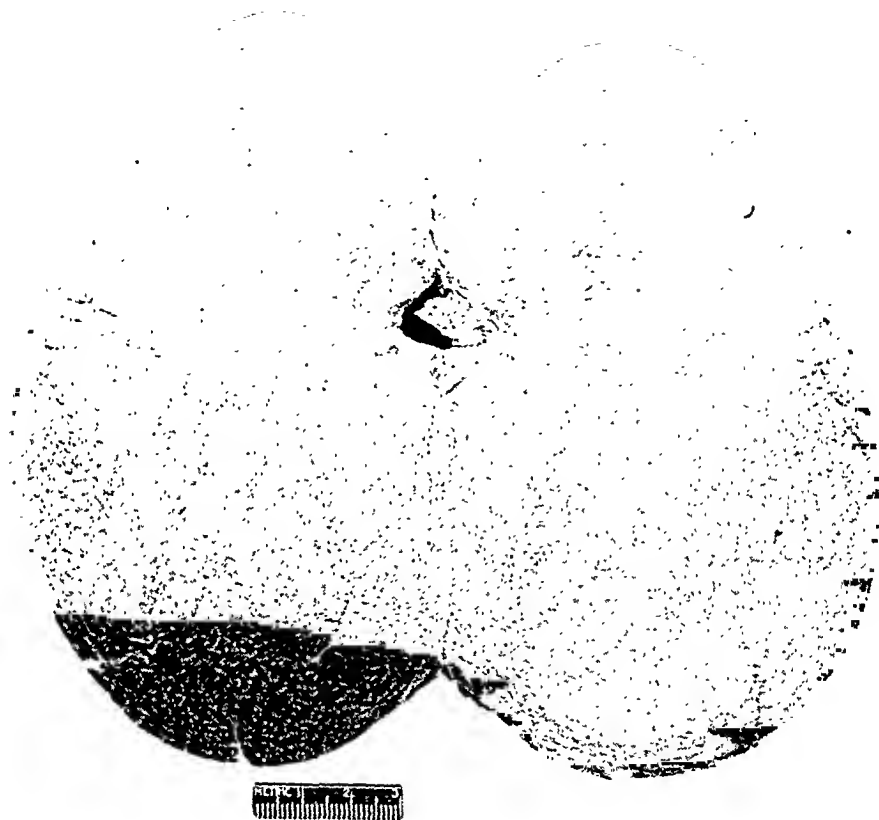


Fig. 2.—Large ovarian fibroma associated with ascites. The white color, fine texture and firm consistency are characteristic.

### Pathologic Data

*Side of Involvement.*—No predilection was noted in this regard, the right and the left ovary showing the same incidence of involvement by fibroma.

*Size of Tumor.*—The average diameter of 312 tumors surgically removed from the 283 patients in this series was 6 cm., with 141 of the tumors exceeding this dimension. Only fourteen of the tumors could be described as being very large (more than 20 cm.). It was interesting to note that the aforementioned average size, with few exceptions, represented a clinical threshold for the production of symptoms. (Most of the larger tumors probably had "outgrown" their early site within the true pelvis.)

*Multiplicity.*—In twenty-eight cases (approximately 10 per cent) multiple ovarian fibromas were encountered. Within this group bilateral single tumors occurred in twenty-three instances, bilateral

multiple tumors in two and unilateral multiple fibromas were present in the three remaining cases. These figures are in keeping with those recorded in the literature but, inasmuch as both ovaries were not always available for study, the figures probably represent too low an incidence of bilateral tumor.

*Color of Tumor.*—Nearly all of the fibromas possessed a whitish or grayish-white color, particularly noticeable on cut section (Fig. 2). In a few instances in which a recent twist of the tumor pedicle had taken place, infarction imparted a reddish hue. A yellow color indicated the existence of fatty metamorphosis, or, as in seven instances noted previously, the necessity for revising the diagnosis to that of theca-cell tumor. The color of ovarian fibromas has long been observed to be so characteristic as to make possible an accurate diagnosis on gross inspection in most instances. Our observations substantiated this view.

*Consistency.*—Two hundred and sixty of the tumors (83 per cent) were solid throughout and unusually "heavy." In several of our more recent cases rough estimation of the specific gravity corroborated our impression that, per unit of volume, ovarian fibromas rank among the most dense of the tumors of soft tissue. Fifty-two of the tumors were associated with cysts of variable size and position. Surface cysts were usually small and possessed of a smooth lining. Central cysts were more obviously of a degenerative type with ragged, irregular walls. Often-times concomitant edema of the tumor and its pedicle was noted. (These central cysts are the "geodes" of earlier investigators and their significance will be discussed in a subsequent section.) The contents of the cysts usually were clear and watery, occasionally bloodstained, and, in a few instances, "fatty." Ovarian tissue was often grossly identifiable in the neighboring surface cysts.

Ten of the tumors were almost completely calcified and in an additional fifteen, "gritty" foci were encountered in sectioning blocks for microscopic investigation.

*Ascites.*—Abdominal ascites in amounts calling for a surgical note as to its presence was a complication of fifty-one ovarian fibromas and constituted one of the most interesting features in this study. Never occurring in association with tumors less than 6 cm. in diameter, it "complicated" no less than 36 per cent of fibromas larger than this established average size. The ascitic fluid varied from  $\frac{1}{2}$  pint (237 c.c.) to more than 3 gallons (11 liters), the quantity being in general proportionate to the size of the causative tumor. In many instances there was a history of repeated reaccumulations of the fluid following previous paracenteses. In six cases the fluid was blood tinged and in these cases there was evidence of a recent twisting of the pedicle of the tumor. In the remaining cases the fluid was clear and chemically appeared to represent a transudate rather than an exudate. In two cases there was concomitant hydrothorax. In a combined clinical and pathologic search for the etiologic "common denominator" producing ascites the following facts appeared to be pertinent: Edema of the tumor or its pedicle or both was present in thirty-one of the fifty-one cases in which there was ascites. (This incidence of edema was twice that observed in the group without ascites.) Central cystic degeneration with or without edema was noted frequently in tumors of the "ascitic group" (Fig. 3) but was rare in the group of cases in which free peritoneal fluid was not observed at the time of operation. In 30 per cent of the cases in which there was ascites, adhesions, probably re-

sulting from ancient twists of the pedicle of the tumor, also were present. Pain was an important clinical feature in this latter group.

*Microscopic Features.*—The microscopic characteristics of ovarian fibroma have been described well by Peterson,<sup>13</sup> Meigs and Cass<sup>11</sup> and



Fig. 3.—Large ovarian tumor associated with ascites. Note the extensive degeneration with formation of cysts.



Fig. 4.—The section made from a small cellular fibroma at its junction with the enveloping cortex shows closely packed spindle cells in "featherstitch" arrangement. The line of demarcation between normal and tumorous tissue is not distinct (hematoxylin and eosin  $\times 100$ ).

others. In keeping with their observations, we found that all of the tumors could be classified into cellular and fibrous types occurring in pure or mixed forms. In all, the basic cell appeared to be the peculiar mesodermal type so characteristic of the ovarian stroma. Moreover, the tumors in general preserved the closely knit "featherstitch" arrangement (Fig. 4) so typical of the normal ovary. In general small tumors were cellular, resembling in this respect ovarian cortical stroma.



Fig. 5.—Fibrous stroma—poor in cellular elements, rich in collagenous fibers (hematoxylin and eosin  $\times 100$ ).

Large examples on the other hand were frequently fibrous (Fig. 5) and even hyaline, suggesting that deposition of collagenous and hyaline substance represented degenerative or "senescent" changes in the maturation process of a basically cellular type. Individual tumor cells were small, thin, spindle units with pointed cytoplasmic processes and narrow, oval, hyperchromatic nuclei running parallel to the long axis. Collagenous and hyaline material surrounded and compressed the cells in many fields. Moreover the hyaline "bands" which have been described as being typical of theca-cell tumor were encountered fairly frequently. When, as was sometimes the case, fatty metamorphosis existed along with hyaline change, some difficulty was encountered in making a microscopic diagnosis of fibroma versus theca-cell tumor. In many instances the plump appearance of the true theca cells was the deciding factor, but in others the clinical history combined with chemical analysis for type of lipid substances was necessary in order to decide the issue.

Ovarian tissue was identified microscopically in about one-half of the cases studied. The demonstration within this tissue of follicles, corpora

lutea and corpora albicantia served as a reminder that ovarian fibromas are extremely rare (if indeed ever found) before the onset of puberty. In the case of small fibromas a layer of "germinal epithelium" invested both ovary and tumor, but with larger neoplasms the capsular investment was fibrous. In no instance was epithelium of a secretory type found on the surface of a fibroma where it might conceivably give rise to ascites. Cystic fibromas, microscopically, were of two types: (1) small fibromas containing multiple small, smooth-walled, superficial cysts, often bilateral; (2) large fibromas with single or multiple cysts, often of fair size, with rough, ragged walls. In the former condition there was often a lining of flattened granulosa cells. These tumors



Fig. 6.—The photomicrograph, made from the tumor illustrated in Fig. 2, shows marked separation of the tumor cells by edema fluid. This picture we have found consistently in fibromas producing ascites (hematoxylin and eosin  $\times 170$ ).

might be classified as the end result of fibrous overgrowth affecting the ovary rather than true localized formation of fibroma. In the second group the cysts appeared to arise through a fusion of zones of edema within the tumor substances—the "geodes" of Coe<sup>6</sup> and other writers on the subject. In the case of large central cysts, even though the walls were sometimes fibrous, interstitial edema was always present in noncystic portions of the tumor.

Including the cases of edema with formation of cysts, the separation of tumor cells by an excess of tissue fluid (Fig. 6) was observed in seventy of the 312 tumors examined. That it was often patchy in distribution, even microscopically, indicated that our observed incidence was probably too low. Significant was the fact that of fifty-one tumors accompanied by production of ascites, forty-nine (96 per cent) showed



edema, usually in marked degree. This appeared in contrast to a 10 per cent incidence of edema in tumors without ascites. Moreover, in this latter group of twenty-seven tumors, although fluid was not present in the "free" state, it was enveloped in thirteen instances within the ragged walls of the degenerative cysts referred to in the foregoing paragraph.

Surface adhesions, present on forty-three tumors, were studied but no positive conclusions were drawn except that the adhesions had resulted from chronic infarction and consequent peritoneal irritation. In several instances such infarction had resulted in the tumors becoming parasitic. In twenty-nine of these forty-three cases there had been a clinical history of attacks of pelvic pain.

Associated pelvic pathologic lesions included a large number of conditions, with uterine fibromyomas leading the list. The ovary in which the fibroma was situated was simultaneously at times the seat of simple cyst, dermoid cyst, tarry cyst, cystadenoma or cystadenocarcinoma, against the development of which fibroma did not confer any apparent immunity. Sarcomatous change was observed in three examples. All three of these cases have been reported previously from the clinic.<sup>4</sup>

*Origin of Ovarian Fibroma.*—Histogenetic studies carried out principally on tumors of small size indicated that ovarian fibromas arose from the spindle cells of the ovarian cortex. Indeed in many instances it was almost impossible to say definitely just where normal cortex ended and tumor began.\* Moreover, as previously indicated, the tumors preserved in fair degree the "featherstitch" pattern of the normal ovarian architecture. Following the hypothesis of Brothers<sup>3</sup> that ovarian fibromas result from the desmoplastic reaction attendant upon ovarian hemorrhage, a search was conducted for the telltale evidence of hemosiderin pigment. Results were disappointing with positive findings in twenty-three instances only. (However, evidence of old hemorrhage often is not seen in corpora albicantia even though one may be sure that hemorrhage was present in the corpora lutea of origin.) The hemorrhage associated with endometriosis was similarly disappearing in its practical nonappearance but the finding in twenty-five ovarian fibromas of endometrial-like glands indicated a possible stimulation for the formation of fibromas. Twenty-three other tumors, originally listed as fibromas, contained so many glands that they were deleted from the present series, under the caption "adenofibromas." Briefly, then, although our studies did not bear out universally the importance of hemorrhage in the histogenesis of ovarian fibromas, the clinical observation that fibromas did not occur before the age of "ovarian hemorrhage" plus the occasional finding of hemosiderin and endometrial glands in fibromas *might* be correlating facts of importance favoring such a view.

### Summary and Conclusions

Ovarian fibroma is the second commonest of the solid ovarian neoplasms. Three hundred and twelve of these tumors accounted for 5 per cent of all ovarian tumors surgically removed at the Mayo Clinic. Ovarian fibroma was never encountered before the age of puberty and this observation has been taken to indicate an origin possibly based on a

\*The so-called fibroma of the corpus albicans appeared in our experience to be a structure totally dissimilar to, and never productive of, true ovarian fibroma.

desmoplastic reaction to the hemorrhage of ovulation or ovarian endometriosis. Fibroma did not produce any specific diagnostic symptoms and rarely was it possible for the clinician to go further than to say "ovarian tumor," "solid ovarian tumor," and so forth. Abdominal ascites (fifty-one cases) and hydrothorax (two cases—syndrome of Meigs) suggested the existence of a malignant process but the patients never presented the picture of cachexia. The complications of these tumors were chiefly those associated with twisting of the pedicle of the tumor—a phenomenon which rarely occurred until the tumor outgrew the confines of the true pelvis.

Pathologically, most of the tumors were solid throughout, white and usually invested by a smooth capsule free from adhesions. Many of the tumors were edematous and a number of these had undergone degenerative changes with central cysts or "geodes." The common denominator relating to both ascites and formation of cysts was a weeping edema effected through partial obstruction of the venous return. Hydrothorax was very rare and appeared to be incidental. (It occasionally occurred from equally obscure causes among patients suffering from ascites of origin other than fibroma.)\* In 90 per cent of cases the tumor was unilateral. Bilateral fibroma-like tumors sometimes proved to be metastatic tumors of the Krukenberg type with the primary neoplasm most frequently in the stomach. A yellowish color suggested theca-cell tumor, especially in cases in which the uterus was large and postmenopausal bleeding was noted clinically. In others the yellow color resulted from fatty metamorphosis. A grayish-brown color and firm consistency were noted in several tumors that later proved to be of the Brenner type. A brownish color and soft consistency indicated malignant change, which occurred in 1 per cent of the tumors studied.

Microscopically, both cellular and fibrous types appeared to arise from the spindle cells of the ovarian cortex with hemorrhage as a possible inciting element. Degenerative changes, such as fatty, fibrous, hyaline and calcareous, took positions of importance secondary to the phenomenon of intercellular edema, which correlated more universally than did gross edema and formation of cysts with the clinical production of ascites. Pelvic lesions other than ovarian frequently accompanied fibroma, which at the same time did not protect residual ovarian tissue from the development of dermoids and other tumors.

### Addendum

Since we looked up the statistics for this paper, a patient suffering from Meigs' syndrome has been operated upon at the clinic. The report of the case is as follows:

\*Meigs and co-workers<sup>12</sup> recently discussed the various hypotheses of origin of ascites from ovarian fibroma. Moreover, in one of their recent cases they demonstrated the apparent ease with which finely-divided particulate matter (India ink) could be carried by phagocytic cells from the peritoneum to the pleura via the diaphragmatic plexus of lymphatic channels. Their work was an outstanding achievement in that it removed from the realm of the mysterious, the phenomenon of hydrothorax occurring as a direct result of fluid within the peritoneal cavity.

The patient, a married woman, aged forty-three years, came to the clinic on November 10, 1943, with a history of having noted a feeling of something present in the lower part of the abdomen in the autumn of 1942. She was able to feel a mass in the right suprapubic region which did not cause any pain but since then it had become larger gradually with much enlargement of the abdomen during the last year. A roentgenogram of the thorax showed that there was fluid in both pleural cavities. Pleural fluid had been aspirated on three different occasions elsewhere. The patient had had few general symptoms except for some dyspnea which was always relieved by the tapping. She had not had any pain, weakness or loss of appetite and her weight had remained the same. Examinations of the blood and urine gave practically normal results. Aside from severe perineal lacerations following the birth of her child, the results of examination were essentially negative. A preoperative diagnosis was a large ovarian tumor—fibroma (?) with ascites and right hydrothorax (Meigs' syndrome); also a rectovaginal fistula.

Right thoracentesis was done on November 13, 1943, and two days later, operation was performed through a low mid-line incision. A fibroma, 15 by 20 by 15 cm. and weighing 1,370 Gm., arising from the left ovary, was found. A considerable amount of ascitic fluid was removed from the abdomen and left salpingo-oophorectomy was performed. The right tube and ovary were apparently normal and were preserved. The uterus was negative. The patient had a satisfactory convalescence and was dismissed from our care on December 2, 1943.

While there is no doubt that it is an interesting finding when present, yet in the great majority of cases of fibroma there is no evidence of fluid in the thorax. However, in many cases in which there are an abdominal tumor and fluid in the thorax but in which the patient otherwise is in good general condition, the possibility of this syndrome must be considered and the patient should be given the advantage of an exploration.

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## THE EFFECT OF PREGNANCY ON BLOOD PRESSURE IN NORMOTENSIVE AND HYPERTENSIVE DOGS\*

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AN IMPORTANT criterion of normal pregnancy in the human being is the blood pressure level. It is therefore not surprising to find a great deal of data assembled on the blood pressure levels in normal pregnant women. While the data are sufficiently clear to lead to the general deduction that the normal pregnant female does not show blood pressure levels outside the normal range and that the changes which do occur are slight, a survey of the literature, excellently summarized by Jensen<sup>1</sup> and Henry,<sup>2</sup> shows that beyond this the findings are not entirely in accord. There are several reasons for this: (a) The differences in the methods and the criteria used in determining the blood pressure levels, (b) the possible inclusion of pre-eclamptic patients, especially those with "subclinical" forms of pre-eclampsia, and (c) the reliance, in many studies, on statistical data from scattered observations on large numbers of women.

In the few studies in which patients have been followed through pregnancy and the puerperium, the results are more consistent. Thus a number of workers, Strassmann,<sup>3</sup> Hare and Karn,<sup>4</sup> Landt and Benjamin,<sup>5</sup> Cohen and Thomson<sup>6</sup> and Hamilton and Thomson,<sup>7</sup> reported the frequent occurrence of a fall in blood pressure from the fourth to the ninth lunar month. They concur that the blood pressure tends to rise again in the tenth month and that the blood pressure usually reaches the normal level in the first week of the puerperium.

Recently, observations have also been made on the effect of pregnancy on the blood pressure in animals. The data in the normotensive animals are not in agreement.

Thus, Corbit<sup>8</sup> noted a drop in blood pressure in the normotensive pregnant rabbit before term, Page and Ogden<sup>9</sup> and Page, Patton and Ogden<sup>10</sup> noted a drop in blood pressure during pregnancy in the rat, while Foa, Foa and Peet<sup>11</sup> reported no change. "Pseudopregnancy" in the rat, according to Page, Patton and Ogden,<sup>10</sup> also led to a blood pressure drop. All investigators report a blood pressure drop late in pregnancy in the hypertensive animal, viz., in the rat (Harrison, Grollman, and Williams,<sup>12</sup> Grollman, Harrison and Williams,<sup>13</sup> Foa, Foa and Peet,<sup>11</sup> in the rabbit (Corbit<sup>8</sup>), and in the dog (Goldblatt, Kahn and Hanzal,<sup>14</sup> Mason, Harrison and Blalock<sup>15</sup> and I. H. Page<sup>16</sup>).

In the course of the past 6 years we have had occasion to measure blood pressures for varying periods on several hundred dogs. Amongst them there were 31 pregnancies in which blood pressure readings were

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obtained during a portion or all of the pregnancy. Thirteen of these pregnancies were in animals with nephrogenic hypertension and 18 were in normotensive animals. All pregnant hypertensives were observed during the entire period of pregnancy. In the normotensive animals this was possible only in six pregnancies, the other 12 animals being pregnant for various periods on arrival at the laboratory.

We have analyzed and integrated the data in an attempt to gain a better insight of the hemodynamic factors which interplay during pregnancy.

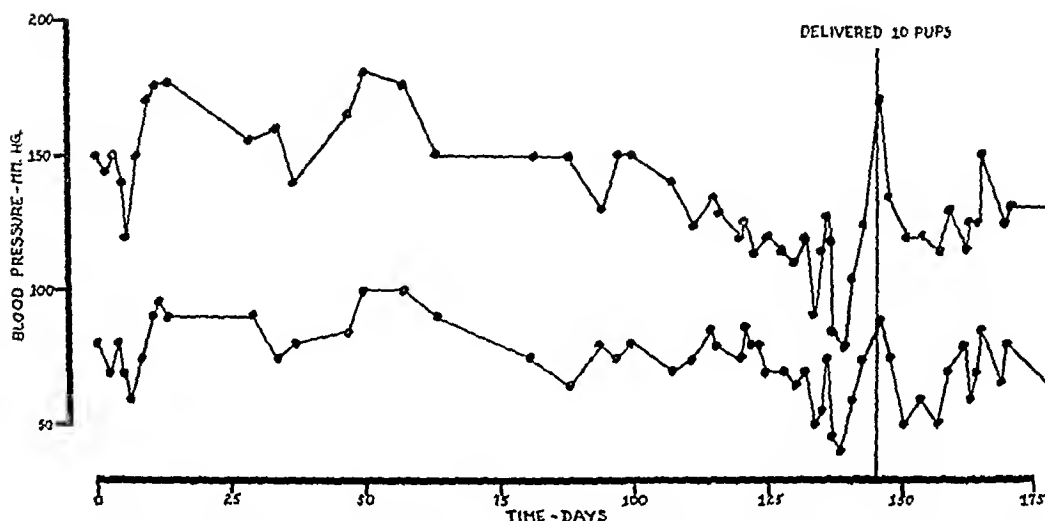


Fig. 1.—Blood pressure changes in pregnancy and in the puerperium in a normal unoperated dog. Systolic pressure above, diastolic below. Discussed in text.

### Methods

Blood pressures and heart rates were obtained one or more times weekly with the Hamilton needle manometer<sup>17</sup> in the manner previously described.<sup>18</sup> In this way accurate photographic records for measurements of both systolic and diastolic pressures were obtained on trained unanesthetized dogs. As the animals approached term, daily pressures were taken in some. Hypertension was induced by partial constriction of one or both renal arteries either with the Goldblatt clamp<sup>19</sup> or with linen ligatures.<sup>20</sup> In one uninephrectomized dog, hypertension was induced by constriction of the renal vein. Blood N.P.N. observations were made by the method of Koch.<sup>21</sup> Records were kept of the behavior and reaction to handling of the animals. Conception was assumed to have occurred 60 days prior to term.

### Results

Data of pregnancy in a normotensive dog are shown in Fig. 1, and in two hypertensive dogs with two and three pregnancies, respectively, in Figs. 2 and 3.\*

(a) *Normotensive Dogs.*—Observations on the blood pressure of the pregnant normotensive dogs, as far as we are aware, have not previously been reported.

\*We had occasion to observe two successive pregnancies and three successive pregnancies in two other dogs.

Fig. 1 shows clearly that the blood pressure in this normotensive dog falls as the animal approaches term and that the level returns gradually to its control value early during the puerperium. This dog delivered 10 viable pups. The fall was particularly striking in this animal, reaching a level of 80/40 mm. Hg as compared with the pre-existing control of about 160/80. The heart rate showed a definite acceleration at

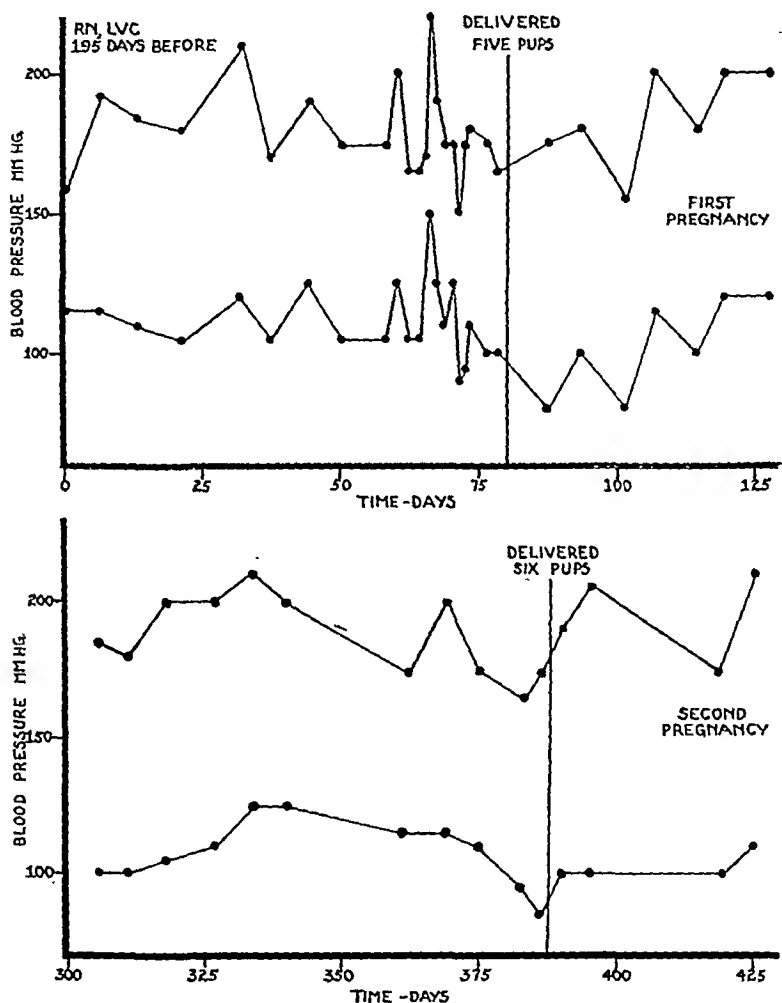


Fig. 2.—Blood pressure changes in two pregnancies in a nephrogenic hypertensive dog. R.N. indicates right nephrectomy, L.V.C., left renal vein constriction. Discussed in text.

the same time. The possibility that this extremely low blood pressure was due to compression of the artery above the point where the femoral artery pressure was obtained while the animal was on its side was ruled out by observing a similar pressure level when the animal was standing.\* The second normotensive unoperated dog observed during pregnancy showed no pressure drop; this dog delivered only two pups. Two other normotensive animals with renal artery constriction but without hypertension showed no blood pressure drop. A third dog with three recorded pregnancies showed a diastolic pressure drop of 15 mm. Hg before term in its second pregnancy, and no drop in the

\*After the puerperium, bilateral renal artery constriction in this dog led to a marked hypertension and uremia, the animal dying with severe pulmonary edema. At necropsy, a very recent myocardial infarction of the left ventricle was seen, a unique finding in the dog.

third.\* Three pups were delivered in each of the three pregnancies without declines in blood pressure, while the one with a slight pressure drop before term delivered eight pups, and the one with the striking fall, ten pups.

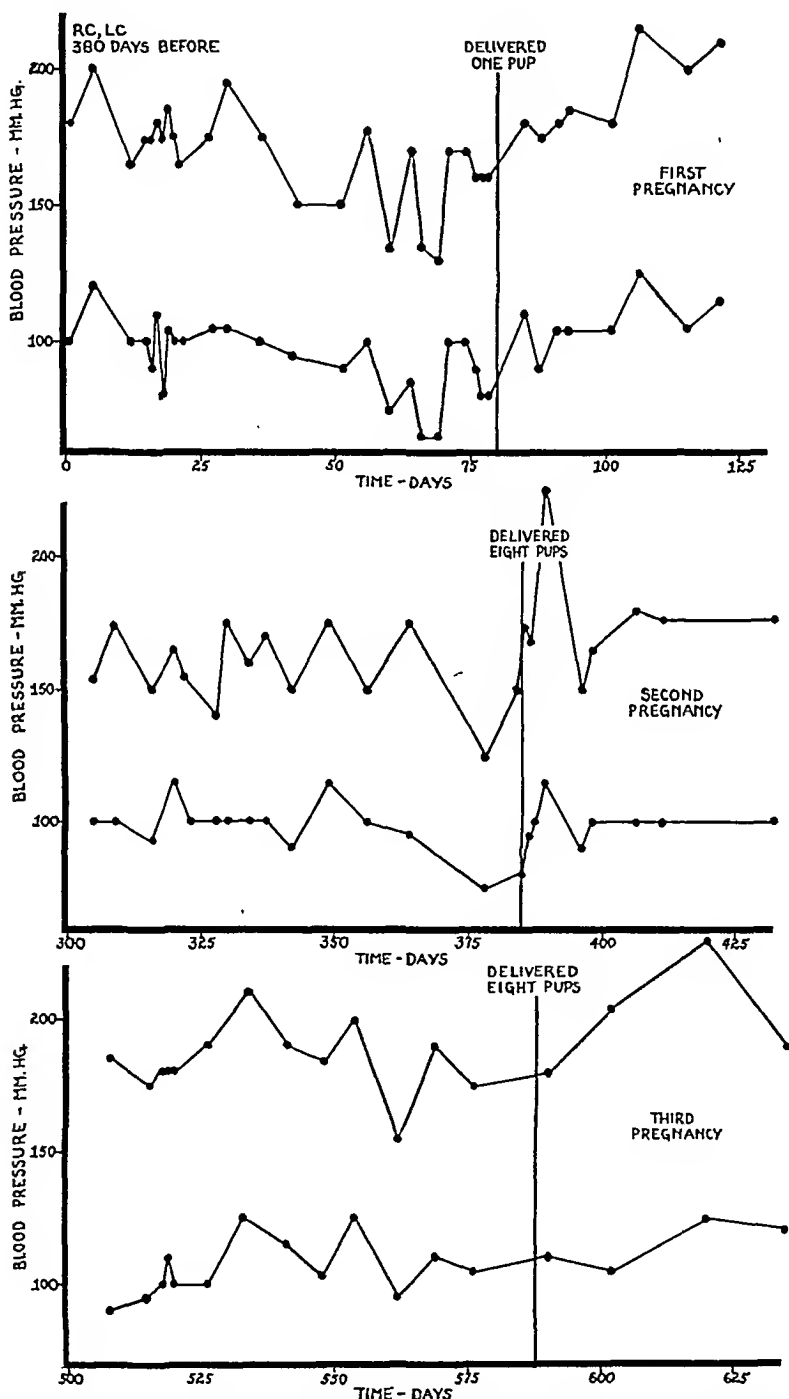


Fig. 3.—Blood pressure changes in three pregnancies in a nephrogenic hypertensive dog. R.C. and L.C. indicate respectively right and left renal artery constriction. Discussed in text.

\*The animal arrived in the laboratory late in pregnancy so that the blood pressure data of its first pregnancy were incomplete.

It would thus appear that when the litter is large the blood pressure may fall before term in normotensive dogs. The variability in our results in the dog may explain the apparently contradictory results in other species of animals with normal blood pressure levels. It is interesting to note that in the animal illustrated in Fig. 1 the low blood pressure level, approaching that seen in surgical shock, had no untoward effect on the animal's behavior. This supports the view that the low blood pressure in shock is not the cause of shock but rather is symptomatic, and that such a low blood pressure can occur in circumstances other than shock.

Further indication that pregnancy has a depressor effect on the blood pressure in normotensive dogs was obtained in the twelve dogs coming into the laboratory late in pregnancy. All of these animals failed to show the "excitement hypertension" usually seen in nonpregnant dogs during the period of training.<sup>22</sup> It is also interesting to note that during pregnancy most of the animals became docile and quiet. This change in behavior may account for the rise in blood pressure after delivery when the dogs became anxious and excitable and apparently greatly concerned over the welfare of their litters.

(b) *Hypertensive Dogs*.—The results in hypertensive dogs are consistent in showing a drop in blood pressure around term. This occurred in 10 out of 13 hypertensive dogs (e.g., first and second pregnancy of Figs. 2 and 3). However, as these figures show, the time of occurrence of the pressure drop varies from the last third of pregnancy with a return to the pre-existing levels before term (viz., first pregnancy, Fig. 3), to a period at or near term (viz., second pregnancy, Figs. 2 and 3) or early in the puerperium (viz., first pregnancy of Fig. 2). The time of occurrence of this drop is not consistent in repeated pregnancies in the same dog. The absence of the blood pressure drop in two of the exceptions may have been due to the small size of the litter; in one the litter consisted of four pups, and in the other no pups were found, the pregnancy having been terminated by abortion. In the third exception the absence of a blood pressure drop was not due to the small size of the litter.

The drop in pressure caused by pregnancy was not only more consistent but was more marked in the hypertensive than in the normotensive animals. It could not be correlated with the presence or absence of tachycardia or with blood N.P.N. changes.

In three dogs, operations designed to interfere with the renal blood supply were carried out during pregnancy to determine if pregnancy modified the blood pressure response to such operations. In one dog in which this was done, abortion of four stillborn nearly full-term pups occurred four days later. The animal then developed a malignant hypertension and died in uremia six days post partum. In a second dog, there was no effect on blood pressure, two viable pups were born 33 days later following a dog fight in which the mother participated. In the third dog, shown in Fig. 4, the renal vascular operation, which was carried out 38 days before term, led to a definite hypertension which abated temporarily before term. We have previously seen malignant hypertension develop quickly in some nonpregnant dogs and have observed the absence of hypertension following partial renal arterial occlusion in others, and can therefore consider the blood pressure effects in the first two dogs as not peculiar to pregnant animals. This is not the case in the third animal whose data are shown in Fig. 4. The temporary decline in blood pressure in the last part of pregnancy in this dog must have been due to the pregnancy.



## Interpretation of Blood Pressure Changes in Pregnancy

Our results on the effect of pregnancy in the renal hypertensive dog are in accord with previous reports described above. Unlike pregnancy in the human hypertensive in which aggravation of the hypertension frequently occurs, pregnancy in the hypertensive animal produces a fall in blood pressure. This effect suggests that experimental forms of hypertension in animals thus far produced are not analogous to many cases of clinical hypertension. Species differences may play a role in this effect.

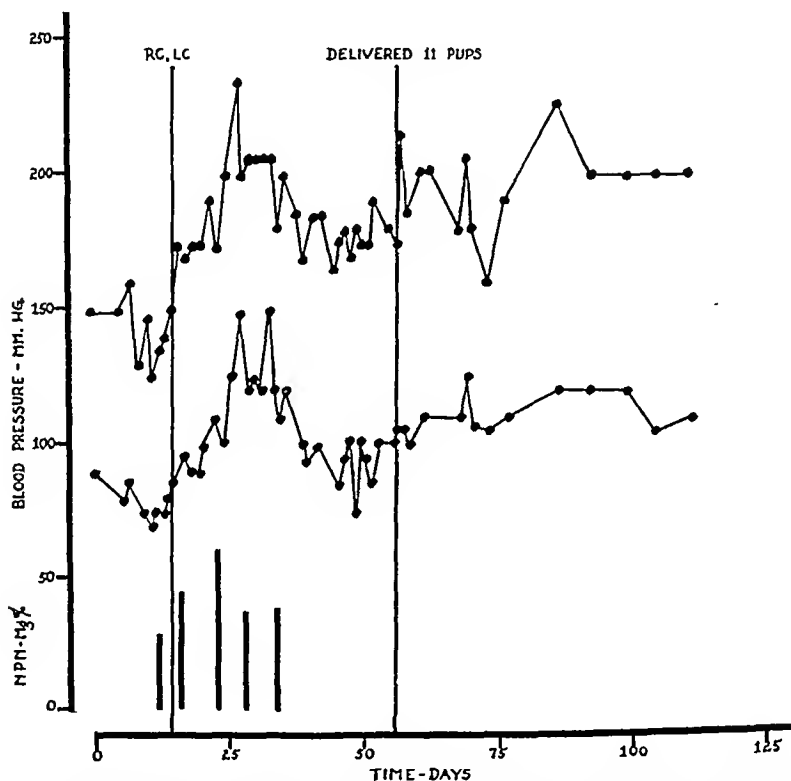


Fig. 4.—Blood pressure changes following interference with renal blood flow during pregnancy. R.C. and L.C. indicate right and left renal artery constriction. Also shown is the blood N.P.N. levels in columns below the blood pressure curves. Discussed in text.

The drop in pressure late in pregnancy or early in the puerperium has been ascribed to some action of the fetal kidneys, overcoming in some fashion the humoral mechanism of renal hypertension of the mother. The fact that we observed a similar fall in the normotensive animal, as did Corbit,<sup>8</sup> and that "pseudopregnancy" has a similar effect (Page, Patton and Ogden<sup>10</sup>) would tend to exclude this mechanism. This view is supported by the report that there is no difference in response to renin between pregnant and nonpregnant animals (Kellar and Sutherland<sup>23</sup>).

Other possibilities suggest themselves to account for this pressure drop. The first is the occurrence of a decrease in the peripheral resist-

ance on a mechanical basis beyond the point where homeostatic mechanisms can cope with it. Another possibility is the production of humoral vasodepressor material in large amount either in the placenta or elsewhere as a result of pregnancy. A third possibility is a decrease in the production of humoral vasoconstrictor materials which help to maintain the blood pressure at normotensive levels and presumably operate also in the presence of renal hypertension.

There is no question at present that pregnancy leads to profound changes in the cardiovascular system. The placenta itself represents a large low-resistance shunt<sup>24-27</sup> which in man may contain up to one-sixth of the blood volume.<sup>25, 28, 29</sup> The placenta grows rapidly in pregnancy and apparently somewhere about midterm its size becomes sufficient to affect the total systemic peripheral resistance. The rapid continued growth of the uterus after this period continues to increase the size of the shunt through it. In the last lunar month the placenta becomes hyalinized, more compact, and the blood flow through it may decrease by as much as fifty per cent. An increase in resistance also is caused at this time by an increase in uterine tone (Reynolds<sup>25</sup>).

These changes in the uterus must be integrated with the striking changes in the general circulation which occur simultaneously. These changes in the cardiovascular system reach their maximum in man at about the ninth lunar month and then regress during the tenth lunar month and in the puerperium (Hamilton and Thomson<sup>7</sup>). There is a striking increase in cardiac minute output (up to fifty per cent) and stroke output in man<sup>6, 27, 30-33</sup> and in the dog,<sup>34</sup> in circulating blood volume in man<sup>6, 27, 35-37</sup> and in velocity of blood flow in man.<sup>6, 38</sup> The blood viscosity is decreased in man,<sup>6</sup> the venous pressure falls slightly in man.<sup>39</sup> Certain changes in particular organs have been noted, viz., the spleen of the dog shrinks in size,<sup>40</sup> the flow in the limbs of man is increased<sup>41</sup> but the flow in the kidney of man as determined indirectly by clearance studies does not change.<sup>42</sup> No evidence of cardiac hypertrophy was obtained in pregnant animals by Van Liere and Sleeth.<sup>43</sup>

It is apparent from the above analysis that the presence of an ever-increasing low-resistance shunt for the first 90 per cent of pregnancy would tend to decrease the effective total systemic peripheral resistance on a purely mechanical basis and so, by itself, would tend to lead to a drop in arterial blood pressure with its maximum at the time when about 90 per cent of the period of pregnancy was reached. This effect is counterbalanced by the increase in circulating blood volume and cardiac output which would tend to keep the arteries filled and so maintain the blood pressure. The homeostatic function of the nervous system operating primarily to cause vasoconstriction of the splanchnohepatic circuit would assist in this process. Ordinarily these factors manage to keep the blood pressure at its normal level for most of pregnancy but in animals this appears to fail to do so late in pregnancy.

While the foregoing explanation may be adequate to account for the blood pressure drop, it requires the assumption that there is a great variability in the time when the placental shunt effect dominates over that of the increased cardiac output and circulatory blood volume. Further, it fails to account for those experiments in which the blood pressure drop first appears in the puerperium.

It is quite possible that the variability in the time of the blood pressure drop in pregnancy is to be accounted for by some humoral mechanism. Either some of the humoral vasodepressor factors evolved during pregnancy become potent at this time or the usual humoral pressor substances helping to maintain the blood pressure become less effective. Endocrine disturbances accompanying pregnancy may release vasodilator substances which might produce the blood pressure changes.

It should be emphasized that despite the marked dynamic alterations which occur in pregnancy, the blood pressure during most of pregnancy is surprisingly little affected. This illustrates anew the normal operation of homeostatic maintenance of blood pressure at a constant level.

### Abortion in Pregnant Dogs

Recently, Dill and his associates<sup>44-46</sup> have reported on the great frequency of abortion and resorption of fetuses in pregnant rabbits and dogs following operative interference with the renal blood supply. Many of their animals developed signs and symptoms which were interpreted as simulating those of the toxemias of pregnancy seen in the human subject. The pathological changes in the liver and other organs were considered to confirm this view.

Blalock, et al.,<sup>47</sup> confirmed the great frequency of abortion and fetus resorption in dogs following interference with the renal circulation. However, these authors considered that the lesions found at necropsy did not resemble those seen in the toxemias of pregnancy but rather resembled those associated with severe renal ischemia.

It has been shown by Greene<sup>48</sup> that spontaneous abortion, associated with characteristic alterations in the liver morphology, occurs in non-operated pregnant rabbits. Furthermore, it is well known that any operation upon pregnant rabbits can readily lead to abortion. For example, we found in a series of nonoperated pregnant rabbits that the simple procedure employed by us to obtain their blood pressure<sup>49</sup> led in every instance to spontaneous abortion.

Similarly in the dog we found that premature delivery late in pregnancy occurred commonly when dogs were subjected to routine nembutalation and devocalization. One of our normotensive pregnant dogs delivered immediately after participating in a dog fight; the two pups born were viable but died 48 hours later. Furthermore, we had occasion to observe the effect of operative interference during pregnancy in several dogs. One dog, subjected to an extensive chest operation,<sup>50</sup> aborted seven nonviable almost full-term pups three days

later. Four other of our dogs were subjected to operations on the renal blood vessels during pregnancy. In two dogs, five viable pups were delivered four days later. A third dog delivered three full-term stillborn pups four days after the operation. This dog then developed a malignant hypertension with a blood pressure up to 210/145 mm. Hg

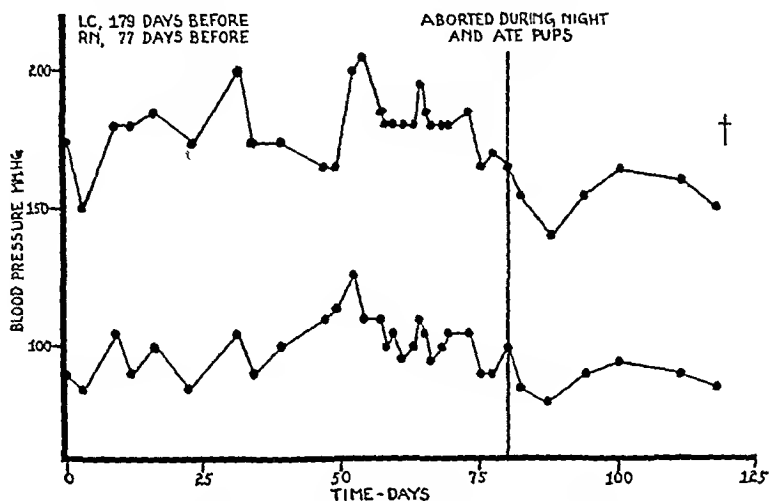


Fig. 5.—Blood pressure changes in an animal with spontaneous abortion. L.C. indicates left renal artery constriction, R.N., right nephrectomy. Discussed in text.

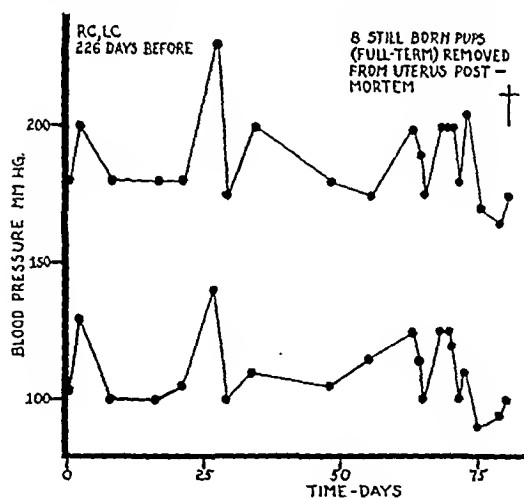


Fig. 6.—Blood pressure changes in an animal with spontaneous abortion. R.C. and L.C. indicate right and left renal artery constriction. Discussed in text.

and uremia and died six days post partum. In a fourth dog (Fig. 4) delivery of 11 full-term viable pups occurred 38 days after surgery, four of the pups dying the same day; the dog survived and maintained the hypertension.

The blood pressure data on two dogs with hypertension which aborted spontaneously are shown in Figs. 5 and 6. The first dog (Fig. 5) was under observation for almost a year, the hypertension was moderate but the diastolic pressure ranged about 15 to 25 mm. Hg above the previous control level. Following a unilateral nephrectomy, the blood N.P.N.

rose to 50 mg. per cent. The dog later became pregnant and showed a slightly elevated blood pressure. The animal then aborted during the night. This was followed by a lowering of the blood pressure level, and the blood pressure rose only slightly in the interval until the dog died 39 days post partum. Before death the legs became progressively weaker until the animal lost the ability to walk about.

The second dog (Fig. 6) was also observed for almost a year. It too had a moderate hypertension, the diastolic blood pressure ranging from 15 to 50 mm. Hg above the control level found before the renal operation, but there was no evidence of uremia. Just before term the blood pressure fell and the heart rate increased. The dog developed convulsions whenever disturbed, became comatose and died. The blood N.P.N. five days before death was normal. At autopsy eight full-term stillborn pups were removed from the uterus. The liver was found to be very small, hard and yellow, suggesting yellow atrophy. Histologically, it showed cloudy swelling and central fatty degeneration with necrosis. The changes in the liver were considered by Dr. O. Saphir of the Pathology Department to be compatible with a severe toxic condition as found in a general toxemia, septicemia or a virus disease.

Our experience with these animals leads us to conclude that operations late in pregnancy, whether leading to malignant hypertension, to benign hypertension or to no change in blood pressure, will increase the susceptibility to abortion in the dog. Abortion occasionally occurs spontaneously in normotensive and hypertensive animals, but further studies will be required before the relation of such abortion to the toxemias of pregnancy is understood.

### Summary

1. The blood pressure in normotensive and especially in hypertensive dogs tends to fall late in pregnancy. The degree of reduction of blood pressure is apparently affected by the size of the litter.

2. It is possible that the blood pressure decline is related to the low-resistance placental circuit which develops during pregnancy. It is also possible that some humoral factor (not involving the fetal kidneys) caused by the maternal endocrine alterations which accompany pregnancy contributes to the blood pressure change and helps to account for the variability in the time at which this blood pressure drop occurs.

3. Surgical or other traumatic intervention during the latter part of pregnancy appears to predispose to abortion in the dog.

We are grateful to the members of the department for help in obtaining the data used and to Miss Louise Friedberg for her suggestions in preparing this report.

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## TRANSPLANTATION OF ABDOMINAL FASCIA FOR THE RELIEF OF URINARY STRESS INCONTINENCE\*

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LOSS of control of urination under muscular effort, such as coughing, sneezing, walking, etc., is a complaint commonly encountered among gynecologic patients. This symptom, termed stress incontinence, often arises following the production of injuries to the supports of the bladder and urethra during the course of parturition, in women who have been previously normal. Less frequently, it is observed in female children with no obvious anatomic defect. They may outgrow it, or it may persist into adult life. The cause of incontinence in such young nulliparous individuals must be ascribed to a faulty development of the poorly understood mechanism which controls the retention of urine in, and the emptying of, the bladder. The occurrence of childbirth in this last group is very apt to greatly aggravate this symptom by superimposing injuries to the supports of the bladder and urethra.

While the more or less standardized gynecologic operations, based on the repair of the supporting structures of the bladder and upper urethra and upon tightening the vesicle sphincters, give excellent results in the relief of this symptom in the majority of instances, most observers report an incidence of failure in from 10 to 20 per cent. Often subsequent operative procedures of a different type may fail to relieve the patient. Failures are particularly likely to occur in individuals whose childhood history suggests a lack of development of the mechanism of urinary control. These patients, unhappy enough before operation, become unhappier and more unfortunate following one or more operative failures.

In March, 1942, Aldridge<sup>1</sup> described an operative technique for the relief of intractable urinary stress incontinence by the use of strips of the abdominal fascia drawn through the rectus muscles and united to form a sling under the bladder neck. This was carried out after well-recognized procedures had been utilized to repair the supports of the urethra and bladder in the preliminary phase of the operation. This technique had been put into practice in the treatment of a fifty-one-year-old woman in whom three previous operations had failed to relieve a marked stress incontinence which had been existent for twenty-nine years. Complete relief of symptoms followed this operation.

This favorable result called to mind several patients in the follow-up clinic of the gynecologic service of Bellevue Hospital, in whom re-

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peated operative procedures of varying types had failed to relieve this distressing symptom. These miserable patients were continuously begging for further surgery, always hoping that one more attempt would produce a favorable result. It was determined to attempt the application of this method in a final effort to improve their control of urination.

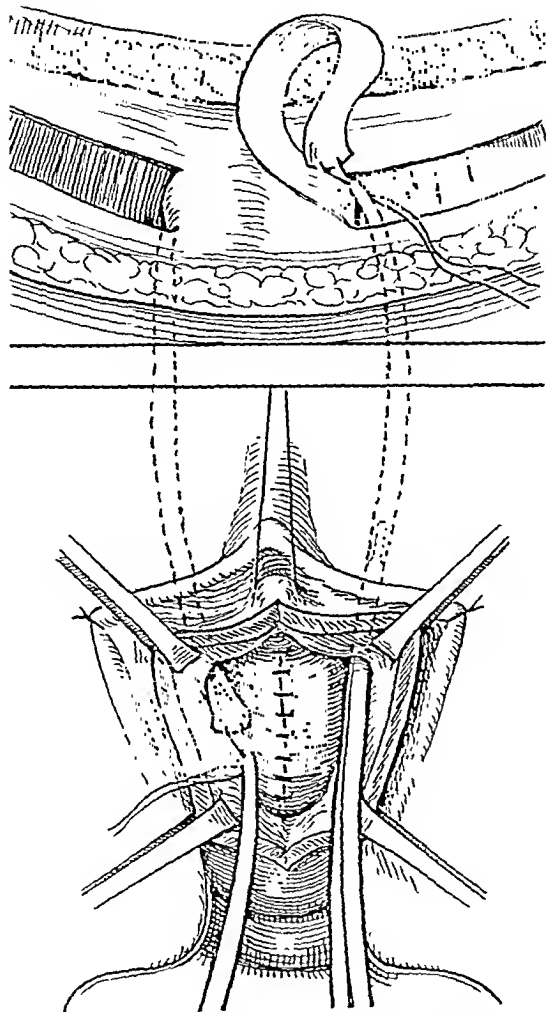


Fig. 1.—The fascial supports of the bladder and upper urethra have been plicated. Through a large curve transverse incision, the center of which lies about 2 cm. above the symphysis, two strips of fascia 7 to 8 cm. long and 2 cm. wide have been freed. Their inner attached ends lie about 1.5 to 2 cm. from the midline. Through their tips have been passed mattress sutures. On the left a uterine forceps has been passed upward between the fascia and the pubic ramus, through the prevesicle space and the rectus muscle. It is grasping the mattress suture. On the right, the fascial strip has been drawn through by means of the mattress suture in the reverse direction to which the clamp was passed.

The technique utilized was almost exactly that described by Aldridge. In only one particular was a departure made from the original procedure. In the first case on which it was attempted, it was found to be impossible to secure fascial strips of sufficient length in order to overlap and suture their ends in the formation of the sling. Therefore, mattress sutures were passed through the ends of the strips, the ends of the sutures then being drawn through the rectus muscles, past



the lateral aspect of the bladder neck, and out of the vaginal incision by a uterine dressing forceps (Fig. 1). By means of these sutures the fascial strips could easily be drawn along the same course. The strips were approximated to form a sling under the bladder neck by simply tying the sutures together (Fig. 2). The bladder neck became elevated and brought forward, close to the symphysis, when this was done. It is believed that this modification simplifies and makes easier the original technique. It was carried out in all four of the patients included in this report. Except for this departure, the reader may be referred to Aldridge's<sup>1</sup> excellent description and illustrations for the technical details.

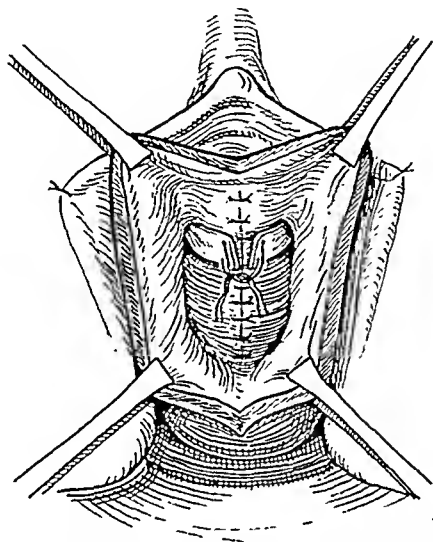


Fig. 2.—The fascial strips are being approximated to form a sling by tying the mattress sutures together. This sling should be fairly tight, and should retract the bladder neck upward and forward behind the symphysis. Actually, at the operation the bladder neck disappears so that the lower border of the sling cannot be seen as depicted by the artist.

In all, four patients have been operated upon, plastic procedures of varying extent having been carried out as indicated in the individual case. Following this, fascial strips transplanted from the abdominal wall, have been utilized to form a sling to support the bladder neck. The individual reports of these patients follow in some detail in order to demonstrate the magnitude of the gynecologic problem and because in one of those patients a most unusual complication arose.

CASE 1.—(No. 8523-43.) Mrs. J. V., 38, para iii, gravida iv, was admitted to the gynecologic service, Bellevue Hospital, on February 20, 1943, for the fifth time, with a chief complaint of stress incontinence. In her first pregnancy in 1924, she was delivered by forceps at home after a labor of five days. Her symptoms date from this event. Full-term pregnancies occurred in 1927 and 1933, and a three-month spontaneous abortion in 1935. Her record showed that she had been admitted in 1930 with the same complaint. At this time a diagnosis of cystocele, relaxed vesicle sphincter and relaxed perineum were made. The cystocele was repaired, the Kelly technique was employed to tighten

the vesicle sphincter, and a perineorrhaphy was performed. No improvement in the incontinence occurred. In 1935, a second attempt to control the symptom was made, utilizing the same procedure except that perineorrhaphy was found to be unnecessary. Again complete failure was the result. In 1940, a third attempt was made utilizing the technique described by Kennedy.<sup>2</sup> No relief was obtained. Six months later, in the same year, a fourth attempt was made to help her by the implantation of a strip of fascia lata under the bladder neck. No noticeable improvement followed.

Physical examination showed a short, stocky, obese woman of healthy appearance. General examination contributed no relevant findings. On pelvic examination, she was found to have excellent support. The anterior vaginal wall was very slightly relaxed. The cervix was posterior, normal in appearance. The corpus was anterior, normal in size and freely movable. The adnexa were negative. There was no loss of uterine support. The general impression of the examiner was that an excellent result had been attained by the previous operative procedures. Nevertheless, on the slightest straining the patient could eject a stream of urine for several feet. Her blood pressure was 120/70; urine examination negative; blood count normal.

On March 5, 1943 she was operated upon, the first step consisting of a wide dissection of the vesicle and urethral fascias. The fascial plane adjacent to the bladder neck was followed upward until the prevesicle space was entered. The fascias were then united in the midline and plicated beneath the bladder and upper urethra. The incision in the anterior vaginal mucous membrane was left open. The patient was then put in the dorsal position and a large transverse incision was made down to the fascia, curving upward on each side of the midline, its center being about 2 cm. above the symphysis. The fascia was cleared of fat and strips 7 cm. long by 2 cm. wide were freed on each side from the external oblique and rectus muscles. The medial attachment of each strip was carefully preserved about  $1\frac{1}{2}$  to 2 cm. from the midline. The outer two-thirds of the fascial defect thus created were immediately repaired with running catgut sutures. The patient was then returned to a lithotomy position and an attempt was made to pass a curved clamp through the vaginal incision along the fascial plane lateral to the bladder neck, through the prevesicle space, and rectus muscle in order to grasp the fascial strip and pull it through in the reverse direction. It was then discovered that no clamp long enough to accomplish this purpose was available. A uterine packing forceps was employed but the strips slipped out of the closed blades on very gentle traction. Finally mattress sutures were placed in the tip of each fascial strip and these were drawn through on each side of the bladder neck. Again difficulty was encountered in pulling down the strips so that they could be overlapped and sutured to form a sling. This was finally accomplished by simply tying the sutures together. This resulted in a marked elevation of the bladder neck. The vaginal mucosa was then closed, and at the same time the remainder of the fascial defect in the abdominal wall was approximated. Eight to ten grams of powdered sulfanilamide were dusted in the abdominal fat, and the skin was closed by interrupted sutures, a small rubber tissue drain being left at each angle. A mushroom catheter was placed in the bladder.

Her postoperative course was uneventful. Moderate serosanguineous discharge was noted from the abdominal wound. The drains were re-

moved on the third day, the incision healing without infection. The retention catheter was accidentally removed on the fourth day and was not replaced because it was found that the patient voided spontaneously. She was kept in bed three weeks. Pelvic examination before discharge showed the vaginal incision healed, the urethra being held tightly against the back of the symphysis. She had perfect control of urination.

This patient has been seen on several occasions since her discharge, the last time being in September, 1943. She is completely relieved of urinary incontinence even when undertaking violent exercises. No weakness is evident in the abdominal wall.

CASE 2.—(No. 22741-43.) Mrs. S. F., aged 42, white, married, para ii, gravida ii, was admitted to the gynecologic service, Bellevue Hospital, for the second time on May 11, 1943, complaining of marked stress incontinence. Her two children, born in 1932 and 1934, had both weighed over 9 pounds at birth. Loss of bladder control was noticeable after the second pregnancy but became much worse in 1940. Her previous admission in April, 1942, had been for the same complaint. At this time a cystocele was repaired, the bladder neck and urethra being plicated following the Kennedy<sup>2</sup> technique. A perineorrhaphy was performed. No relief had followed this procedure. Her menstrual history was normal; her blood pressure was 170/105; the laboratory data were irrelevant.

Except for the blood pressure findings, her general physical examination proved normal. The abdominal examination was negative. On pelvic examination, she was found to have adequate perineal support; moderate relaxation of the lower half of the anterior vaginal wall was noted; the cervix was posterior, flush with the vaginal vault; the corpus uteri was anterior and not enlarged; the adnexa seemed normal.

On May 15, 1943, she was operated upon, the identical procedure being used that has already been described in Case 1. On this occasion the fascial strips were drawn down on each side of the bladder neck by mattress sutures passed through their tips, by preference and not in desperation. The strips were united under the bladder neck by tying the sutures together. A median episiotomy had to be performed in order to gain proper exposure, and this was closed at the conclusion of the main operative procedure.

This patient had an uneventful postoperative course. She voided spontaneously and never required catheterization. She was examined on the seventeenth postoperative day, just before discharge, at which time the vaginal and abdominal incisions were found to be healed by primary union. The bladder neck was well supported and the urethra held snugly against the back of the symphysis. She had perfect control of urination.

She has been seen several times since discharge, the last occasion being on December 6, 1943, and reports that she is absolutely free of symptoms except that she is aware of slight suprapubic tugging when she coughs. No weakness of the abdominal wall is present. Pelvic examination shows an excellent anatomic result.

CASE 3.—(No. 22794-43). Mrs. S. T., aged 51, a married, white female, para iii, gravida v, was admitted to the gynecologic service, Bellevue Hospital, on May 11, 1943, for the fourth time complaining of stress incontinence, urgency of urination and the protrusion of a mass

from the vagina. Her children had been born without difficulty in 1907, 1917, and 1919, their weights at birth being unknown. She had had two spontaneous miscarriages. In 1926 she had had a left nephrectomy for chronic suppurative nephritis. In 1928 she underwent cholecystectomy. About 1935, at the age of forty-three, the onset of hypertension was noted and between 1938 and 1941 she was treated with digitalis for mild heart failure.

On the occasions of her first admission in April, 1938, she complained of frequency of miction of five to six years' duration and of stress incontinence for the preceding eighteen months. She was found to have a large cystocele, a relaxed perineum and multiple fibroids. At her operation, the cystocele was repaired, a Kelly stitch being utilized to tighten the vesicle sphincter. A perineorrhaphy was performed, following which a supravaginal hysterectomy was carried out.

Following this admission, her cystocele recurred very rapidly and she had no relief from her urinary symptoms. She was readmitted in January, 1939, when the cystocele was once more repaired, the bladder neck and upper urethra being plicated according to the Kennedy<sup>2</sup> technique. In May, 1941, because of failure to relieve her symptoms and the second recurrence of cystocele, she was readmitted. The cystocele was again repaired and an attempt was made to interpose the cervical stump beneath the base of the bladder. This operation proved equally unsuccessful.

Physical examination revealed an obese elderly female. The heart was clinically enlarged and a systolic murmur could be heard over the entire precordium. The rhythm and rate were normal and no suggestion was present of cardiac decompensation. Abdominal examination revealed scars in the upper right quadrant, in the left flank and in the suprapubic region. On pelvic examination, there was found a large cystocele with partial prolapse of the cervical stump and vaginal vault. A rather advanced degree of atrophy was noted. Her blood pressure was 240/110. The laboratory findings revealed nothing noteworthy.

She was operated upon May 13, 1943. At this time the cystocele was again repaired, the broad ligaments were approximated in the midline following the excision of the cervical stump, and the fascial supports of the posterior vaginal wall were dissected out and approximated. The extensive vaginal incision was then closed except for the anterior wall and the operation was concluded by the transplantation of fascial strips from the abdominal wall according to the previously described method. The anterior vaginal wall was then closed and the vagina was packed with plain gauze. This extensive procedure took over two hours to perform.

Immediately following the operation the patient showed a moderate degree of shock. Her blood pressure was 105/65, her pulse 50, and her color poor. She was given a transfusion of 500 c.c. of bank blood, and later an infusion of 1,000 c.c. of 5 per cent glucose in saline. She rapidly responded to this, appearing much better the next morning with a blood pressure of 160/90, a pulse of 75, and a temperature of 99° F. Because of frequent vomiting, she was given 1,000 c.c. of 5 per cent glucose in saline. However, it was noted at this time that her urinary output had markedly decreased. Catheterization on the evening of her operation yielded 200 c.c.; at 5:30 A.M., on the first postoperative day, 90 c.c. This trend rapidly increased, only 20 c.c. being obtained at 7 P.M., an additional 20 c.c. being voided at midnight. On the second

day postoperative, May 15, no urine could be obtained on repeated catheterizations. The patient continued to vomit and was given several infusions. Because the onset of this condition was gradual, some urine being excreted into the bladder during the first thirty-six hours after operation, it was felt that the left ureter must be occluded by edema rather than ligated. The possibility of anuria due to transfusion was considered but no evidence of hemolysis could be found. This situation was made even more serious because the patient had only one kidney, her right, the left having been removed in 1926. An intravenous pyelogram was obtained and no dye could be visualized in the right kidney pelvis or ureter. A blood chemistry showed a nonprotein nitrogen of 33 mg. per cent. It was decided that the patient should be observed a little longer in the hope that the edema would subside. On May 16, the third postoperative day, no urine could be found in the bladder on catheterization. Her nonprotein nitrogen was reported as 43 mg. per cent. She was subjected to cystoscopy at which time the right ureteral orifice was visualized with difficulty because the floor of the bladder was elevated by its new fascial support. Fairly marked edema was present about the right ureteral orifice and attempts to introduce catheters and bougies resulted in failure. On May 17, the fourth postoperative day, no urine was found in the bladder. The nonprotein nitrogen had risen to 75 mg. per cent. The patient was stuporous and showed pallor and rather a marked edema.

It was felt by both the urologic and gynecologic departments that radical steps must be taken in order to prevent catastrophe. The choice lay between the removal of all sutures in the operative area for the relief of the evident edema, or drainage of the right kidney until the edema began to subside. The hazard of the former procedure lay in the fact that sutures could not be replaced without risking a recurrence of the edema, making the probability of a tremendous postoperative pelvic hernia almost certain. The latter course was therefore decided upon.

The patient was taken to the operating room and the right kidney was exposed. A double ureter was found, both the ureters and the kidney pelvis being markedly distended and tense. The ureter was aspirated and urine was obtained under pressure. A moderate-sized nephrostomy tube was inserted through the kidney parenchyma and urine immediately began to drain. The wound was closed after sprinkling sulfathiazole powder between its layers. The patient was returned to the ward in good condition.

In the next six hours 700 c.c. of urine passed through the tube. Immediate improvement followed. She began to take fluids well and this was supplemented by 2,500 to 3,000 c.c. of fluids by infusion daily. Her nonprotein nitrogen dropped to normal levels. By May 20 (seven days postoperative, gynecologically; three days postoperative, urologically) her condition was excellent. On May 21, exactly eight days after the primary operation, she began to pass urine in small amounts from the bladder. On May 25, she passed 325 c.c. in a twelve-hour period; during this same period the drainage from the nephrostomy tube gradually diminished. On June 1, fifteen days after the nephrostomy, she developed a fever of 103° F. due to a urinary infection, but this rapidly cleared up under mandellie acid therapy. On June 13, twenty-seven days after the nephrostomy and thirty-one days after the primary procedure, the nephrostomy tube fell out and was not replaced. This

wound rapidly closed. She was examined just before discharge, at which time the abdominal, vaginal and nephrostomy incisions were found to be well healed. Excellent pelvic support was present, the vaginal vault being held at a high level, the bladder well supported, and the urethra fixed snugly against the back of the symphysis. Intravenous pyelography done before discharge showed moderate dilatation of the right ureter and kidney pelvis.

The patient has been seen on several occasions, the last time being December 4, 1943, and shows an excellent anatomical result with no evidence of recurrence of her former lesions. She has perfect control of urination. Her only complaint consists of occasional slight pain in the region of the right kidney. Intravenous pyelograms have shown a slight persistent dilatation of the right ureter and kidney pelvis.

Encouraged by these results on patients not cured by one or more previous operations, the question as to whether this procedure might be utilized as a primary measure in the treatment of stress incontinence arose. Certainly it could be strongly considered as a primary procedure if the chance of cure by other operations appeared questionable or unlikely. Fortunately, such a case presented herself shortly after these patients had been treated and observed.

CASE 4.—Mrs. M. T., aged 45, married, white, para ii, gravida iii, presented herself, complaining of leakage of urine on coughing, sneezing and walking, which had been present to an almost disabling extent for ten years. Since earliest childhood she had suffered from defective control of urination but this had become much more pronounced after the birth of her children, now twelve and sixteen years old. At present she was only completely continent on sitting and lying down. On walking, she immediately began to dribble urine and this became more pronounced on the slightest exertion. She constantly wore a cotton pad to protect herself. Her general health was excellent and she had had no previous operation. Her menstrual history was normal.

Physical examination showed a short, obese woman who appeared in excellent health. General examination revealed no significant findings. On pelvic examination, she showed a moderate cystocele, a relaxed perineum and a moderate degree of rectocele. A Bartholin cyst was present in the right labium. The cervix was posterior, well supported and normal in appearance. The corpus uteri was anterior and not enlarged. The adnexa were normal. Blood pressure was 120/70. The laboratory findings were irrelevant.

This patient (716,559) was admitted to the Sloane Hospital on August 4, 1943, and operated on the following day. The procedure already outlined in Case 1 was carried out, following which the right Bartholin cyst was excised, the rectocele was repaired, and a perineorrhaphy was performed.

Her first postoperative day was marked by a rise in temperature to 102° F., but thereafter her course was practically afebrile. Catheterization at regular intervals was employed until August 17 (the twelfth postoperative day) because of inability to void. During this time sulfanilamide 0.5 Gm. was given three times a day to prevent cystitis. During the next five days she complained of urgency and frequency. She was examined on the day of discharge, August 23, at which time the abdominal and vaginal incisions appeared well healed. The urethra

was tight against the back of the symphysis, the bladder neck being high and well supported. Her perineum showed an excellent postoperative result.

She has been seen on several occasions since leaving the hospital. At the last visit on December 8, 1943, she stated that for the first time in her life she had complete control of urination. She was able to undergo all kinds of exertion with no evidence of leakage, usually voiding voluntarily without urgency at three- to four-hour intervals.

Little comment need be added to the details contained in the outlines of these four cases. In the opinion of the writer, the outlook for improvement or cure in all four cases was dubious had they been treated solely by the usual gynecologic procedures. The value of using transplanted fascial strips from the abdominal wall in addition to such procedures is demonstrated amply by the fact that all four patients show a perfect symptomatic result. It may be said that the follow-up on these patients is too short. That cannot be avoided since they have all been cared for during the past year. Observation will be continued with high hopes that the early results will be permanent.

### Summary and Conclusions

1. Fascial strips from the abdominal wall have been utilized to form a sling under the bladder neck after the performance of procedures designed to improve the support of the bladder and upper urethra.

2. Three patients, with a chief complaint of urinary incontinence, totaling between them eight operative failures with a variety of methods, have achieved perfect symptomatic and anatomic results by means of this procedure.

3. One patient, whose background of poor urinary control in childhood suggested difficulty in the operative correction of incontinence, has apparently been cured.

4. The occurrence of an interesting complication has been described and its treatment outlined.

5. The operative technique of this procedure, originally proposed by Aldridge, has been slightly modified and, it is to be hoped, simplified and improved.

6. Additional evidence is presented that this procedure is of the greatest value when other methods have failed. Further, it is suggested that the operation may be used as a primary procedure when study of the patient suggests that the usual operations have a strong possibility of failure.

#### NOTE:

CASE 1.—Mrs. J. V. (No. 8523-43), Bellevue Hospital, returned for a follow-up visit on December 15, 1943, the day after the above report was presented. She stated that, with the return of cold weather, she had noted slight incontinence on going out of doors. This also occurred when she lost her temper with her children. On violent coughing, she also lost a few drops of urine. She felt quite

satisfied, however, with the marked improvement since her operation and showed no desire for further surgery. Examination showed a well-healed abdominal incision with no evidence of hernia. Pelvic examination showed an excellent post-operative result, the bladder being firmly fixed high up and close to the neck of the symphysis.

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### Discussion

DR. GEORGE W. SLAUGHTER.—The fact that a serious complication occurred in one case should in no way detract from the usefulness of the operation. Temporary unilateral anuria, I believe, is probably a frequent transient complication in many gynecologic operations due to edema of involved tissues with resultant pressure on a ureter. Unless, as in this case, there is only one functioning kidney, the condition is never noted and spontaneous recovery results as soon as the edema subsides. Apparently no damage ensues as long as the involved kidney remains uninfected.

As Dr. Studdiford has pointed out, three possible methods of attacking this problem were at hand. First, a ureteral catheter might be passed to the kidney. This was attempted, but because of angulation a catheter could not be introduced into the ureter. Protracted attempts might easily have resulted in additional edema.

The second procedure, the removal of the sutures, would certainly have destroyed part, if not all that the operation was to gain, with no certainty that extrinsic pressure on the ureter would be relieved.

The third method, a nephrostomy, although it would necessitate subjecting the patient to a second operation, would surely bear fruit. My opinion was that this was the better choice, since it is one of the simplest of all renal operations and can be performed in about twenty minutes. There was every indication in this case that the ureter was being compressed by edema, rather than that it had been ligated, as evidenced by the gradual diminution of the urinary output rather than a sudden stoppage. Nephrostomy would, however, have in any case been the next step, even though the ureter never again became patent.

DR. ALBERT H. ALDRIDGE.—Progress in the development of surgical techniques to cure urinary incontinence by transplantation of muscles and fascia dates back to about 1900. For this purpose at least seven different muscles have been transplanted either alone or in combination with strips of fascia.

A matter of importance is how well transplanted fascia will stand the test of time. The patient reported when the technique used by Dr. Studdiford was first described is now two and one-half years from operation and is still free of symptoms. In the meantime I have used this technique in four additional cases. Details regarding these cases will be reported later. Briefly, it may be stated that results in two of the four cases appear to be entirely satisfactory. A third seems to have a good result from the mechanical standpoint but has slight difficulty at times, probably from bladder irritation due to a persistent urinary tract infection. The infection started following a previous vaginal plastic operation for the same condition, was present at the time of her last operation and has not been entirely eliminated by subsequent treatment. When the urinary infection is kept under control with treatments, she is entirely continent for long periods of time. The fourth patient in whom this technique was used is emotionally unstable and has been under the care of a psychiatrist. When she fails to sleep well or is unusually disturbed emotionally, she occasionally loses a small amount of urine on



getting out of bed in the morning. Otherwise, she is entirely free of bladder symptoms and obviously has no real stress incontinence of urine at any time.

Experience has proved the importance of certain points in the management of these cases. Urinary tract infections should be eliminated as completely as possible before undertaking to relieve urinary incontinence by surgical means. In general, fascial transplantation to relieve urinary incontinence should be used only for patients in whom vaginal plastic operations have failed. It should always be used in conjunction with the usual vaginal plastic procedures for incontinence and should never be regarded as a substitute for them.

I have found a pelvimeter to be helpful in determining the length of fascial strips to be transplanted. With one tip of the pelvimeter placed at the proximal end of the urethra in the vagina, and the other on the abdominal wall, it is not difficult to estimate the length of strips that will be needed to form a fascial sling beneath the urethra.

Dr. Studdiford has recommended the use of mattress sutures in the distal ends of the fascial strips to facilitate drawing them backward into the vaginal wound. I have used this same procedure and have found it helpful.

Dr. Studdiford has apparently also gotten satisfactory results by tying the mattress sutures in the ends of the fascial strips together beneath the urethra instead of overlapping the distal ends of the strips and fixing them together by additional sutures. Success with this technique must depend upon a permanent fascial sling beneath the urethra. For this reason careful fixation of the free ends of the fascial strips to each other by overlapping and careful suturing would seem important.

In completing the fascial sling beneath the urethra, it has been found that it should be made snug enough to give additional support to the proximal end of the urethra and to be certain of immediate pull forward whenever the recti muscles contract with any strain such as lifting, coughing or sneezing.

DR. JOE V. MEIGS (by invitation).—When looking at the urethra of a patient with incontinence, the orifice points to the ceiling and there is a falling down of the urethra from behind the symphysis. We now begin most of our reconstructive surgery by means of a total abdominal hysterectomy after which we turn the patient around and repair the perineum. For this reason it is necessary to suspend the urethra in a little different way.

In four cases I have done a total hysterectomy and after closing the peritoneum I entered the space of Retzius, pulled the bladder up and exposed the urethra. This is very simple to do and it is very easy to visualize the urethra. It is, however, difficult to get the urethra free from the vaginal wall from above.

In the four cases I was able to go beneath the urethra and in these I took a long strip of the abdominal rectus fascia, threaded it under the urethra, brought it up and attached it to the rectus sheath on the other side. In two of the cases the results were not good at the end of three months, but at the end of nine months, there is a good result in both instances.

The third patient I operated upon by the same method is so continent that I had to dilate the urethra. This patient could void only by placing two fingers in the vagina, one on each side of the urethra, and pulling upward. This patient has had three urethral dilatations and is perfectly comfortable. The fourth patient is temporarily lost to our clinic.

It seems to me that the success Dr. Studdiford and Dr. Aldridge have had is due to the fact that they have repaired the urethra from below, as well as having used a fascial band. In my cases nothing at all was done to the urethra, and in three patients, it worked well. I think the great contribution is the combination of the two operations—a plastic and a fascial sling. I was of the opinion that all that would be necessary would be to suspend the urethra, but I do not think that is sufficient.

DR. FREDERICK C. HOLDEN.—At the time Dr. Aldridge presented his paper, we had on the gynecologic service of the Jersey City Medical Centre, a patient who had been operated on twice in the preceding year—once by a urologist and once by a gynecologist—for urinary incontinence, and she was unimproved after each operation. There was no bulging of her anterior wall, but she had complete urinary incontinence.

It was my good fortune to hear Dr. Aldridge present his paper just during the time that we had her under observation. We operated upon her according to the technique described by Dr. Aldridge, and obtained a perfect result. We saw her in the return clinic several times, the last examination being seven months post-operative, and she reported complete control of her urine under all circumstances.

DR. JOSHUA WILLIAM DAVIES.—It is my belief that the use of fascia alone as a transplant around the urethra will not give satisfactory results as an operation for incontinence. Dr. Studdiford has very accurately reconstructed the capsule of the urethra as is shown by his pictures, and if he would utilize the bulbocavernosus muscle as he reconstructs the central body of the perineum, I feel certain that he would secure satisfactory results in 95 per cent of his cases without using the fascial strips.

DR. INGLIS F. FROST.—In some cases where recurrences have occurred there has been, at times, an insufficient preliminary study of the urethra in its relation to the bladder. Dr. Kennedy has clearly shown in his x-ray graphs that the length of the urethra in the incontinent woman, is in disproportion to the neck of the bladder. To obtain a cure in these cases, two factors are important; first, the restoration of the urethra to its normal length and second, mobilization of the bladder in its new position until healing had occurred.

We have used Dr. Kennedy's instrument in numerous cases. It is made of vitallium metal and is composed of two sections, one of which carries gauze in the vagina and retains it. The other acts as a retention catheter. The vitallium metal does not become soiled and no urinary deposits occur. The iodoform packing may remain in situ for at least eight days, and thus it acts as a splint to the anterior wall. Constant drainage of the bladder with the vitallium catheter keeps the bladder empty and gives it a chance to heal at the point where you want it to heal.

DR. JAMES R. MILLER.—I would like to say a word in support of the method used by Dr. Hepburn. I have done three cases of complete eversion prolapse of the urethra by this method. The operation is simple and can be done in fifteen or twenty minutes. It has given perfect results in the three cases in which I have done it. The first case was in a woman of 70 with a total prolapse and a large mushroom slough of the urethra. This was pulled back as described by Dr. Hepburn and sutured to the posterior surface of the symphysis and the roof of the bladder above the trigone was sutured to the lower undersurface of the fascia above the symphysis. Later, a LeFort operation was done for the prolapse. That patient has now gone five years and her condition is good.

It is very simple to suture the urethra to the symphysis. A very important step in this operation is to place a drain on each side, to form scar tissue, a point which Dr. Hepburn emphasizes. I hope some day to see this operation for prolapse of the urethra displace the old Whitehead type of procedure.

# CAPILLARY COUNTS, CAPILLARY DISAPPEARANCE PRESSURE AND CUTANEOUS LYMPHATIC FLOW IN NORMAL PREGNANCY\*

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ANNA CALLAGHAN, PHILADELPHIA, PA.

*(From the Robinette Foundation, and the Medical Clinic of the Hospital of the University of Pennsylvania, and the Department of Obstetrics of the Pennsylvania Hospital)*

PREGNANT women frequently experience difficulty in water metabolism. Sometimes they develop hypertension which may or may not subside after delivery. Such a clinical situation offers obvious opportunities for the study of hypertension. Most persons who develop hypertension are first available for study after the hypertension is well established. The pregnant woman is more or less constantly under medical observation and therefore may offer a unique opportunity to study a patient with developing hypertension.

In the present study certain methods which have been applied to the study of patients with hypertension are employed in the study of women in normal pregnancy. These methods include:

1. Capillary counts before and after histamine, by the method first reported by Roberts and Griffith<sup>1</sup> and later by Griffith, Roberts and Corbit.<sup>2</sup>

2. Capillary disappearance pressure (formerly called minute vessel pressure), as described by Griffith, Roberts and Corbit.<sup>3</sup>

3. Cutaneous lymphatic flow, as first described by McMaster<sup>4</sup> and later used by Griffith, Roberts, Rutherford and Corbit.<sup>5</sup>

The present report deals only with women in normal pregnancy without hypertension. It will take somewhat longer to collect data on a corresponding series with hypertension, and the subjects thus far studied are too few to permit their inclusion here.

## I. Capillary Counts, Before and After Histamine

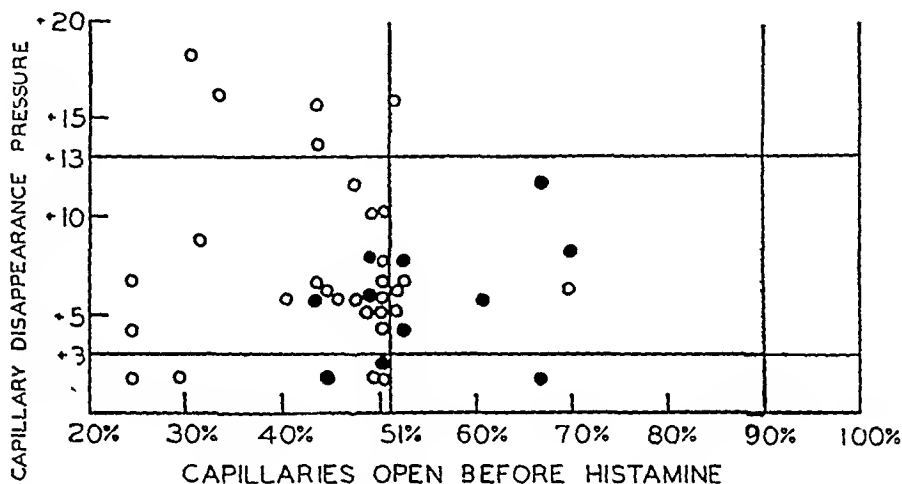
The extensor surface of the forearm is used. A circular die is inked and pressed on the skin so that its inked impress encloses an area of normal skin of approximately 2 sq. mm. A drop of cedar oil is placed on this area and the open capillaries counted, using a microscope with Ultrapak attachment as previously described.<sup>1-2</sup> After a count has been made, a drop of 1:1,000 histamine is placed near the area under observation and a needle pricked through the drop. The flare which

\*Read at a meeting of the Obstetrical Society of Philadelphia, March 4, 1943.

<sup>†</sup>Atwater Kent Fellow in Medicine.

subsequently develops includes the area under observation and the capillary count in it is repeated. The count after histamine is considered to represent 100 per cent of the cutaneous capillaries of that area, and the per cent open before histamine is thus calculated. For example, if, in a given area, 13 capillaries are open before and 26 after histamine, then 50 per cent of the capillaries in that area were open before histamine. A division has been made as follows:

1. Persons with 90 to 100 per cent of their capillaries open before histamine. This group is definitely abnormal and is said to have diminished capillary mobility. It may mean that a degenerative process has involved the capillaries or simply that there is some cause for initial dilatation, as polyeythemia, hyperthyroidism, etc.



recorded is that which when present in a transparent chamber in contact with the skin is just sufficient to cause the disappearance of microscopically observed cutaneous capillaries. The cutaneous area used is the extensor surface of the forearm. While by this method pressure readings can be repeated with variations of not more than 2 mm. of mercury by the same or by different observers, there is considerable doubt as to just what pressure is being measured. On purely theoretical grounds, it seems obvious that it cannot be true capillary pressure. Under conditions of flow, the pressure required to stop flow (or empty a tube which is part of a system of branching tubes) will be the pressure at the nearest bifurcation of the system that has an unblocked branch.

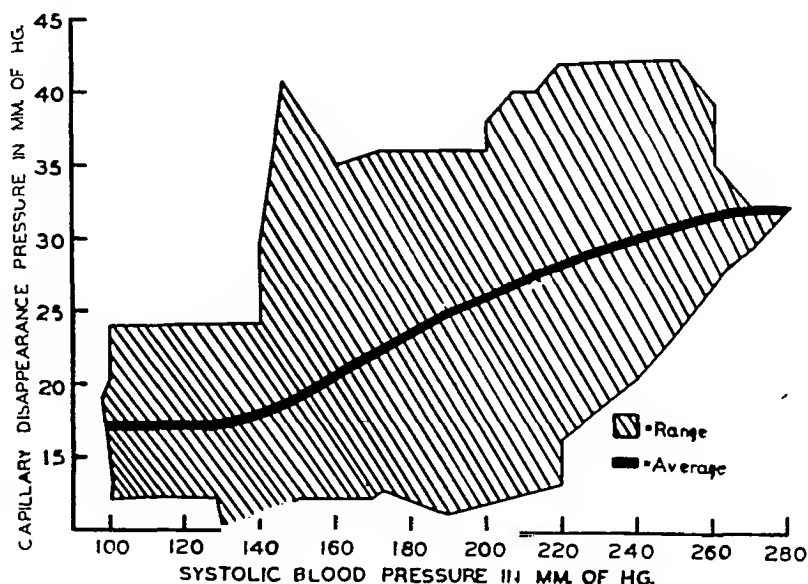


Fig. 2.—Showing the range and average capillary disappearance pressure in subjects with varying systolic blood pressure.

This, most likely, is the precapillary arteriole. It has been shown<sup>3</sup> that this pressure will rise to correspond to an increased venous pressure, produced by inflating a blood pressure cuff about the upper arm, and also that it will rise after local procedures, as the injection of histamine. In these respects it behaves like true capillary pressure. The term originally applied<sup>3</sup> was "minute vessel pressure" and it was stated that "skin elasticity and resistance may interpose a tangible, but fairly constant factor." More recently, however, evidence has been collected suggesting that extravascular factors may affect pressure readings more than was originally thought, and on this account the term "capillary disappearance pressure," a term that is purely descriptive, has been adopted to replace the term "minute vessel pressure." The reasons for this will be reported, in detail, elsewhere.

Fig. 2 shows the range and average of capillary disappearance in persons with normal and with elevated blood pressure. This chart is

based upon observations on 230 subjects, 71 with normal blood pressure and the remainder with high blood pressure. It will be seen that, for persons with systolic blood pressure below 140 mm. of mercury, the range of capillary disappearance pressure is 10 to 24 mm. of mercury, the average is 17, and the standard deviation is 3.7.

If the measurement of capillary disappearance pressure be repeated in the flare area of a histamine wheal, using the technique described in "capillary counts" it will usually be found that the pressure is higher by 3 to 13 mm. of mercury. Occasionally apparently normal subjects will fail to show any change after histamine, but when this is seen associated with diminished capillary mobility, it is thought to suggest sclerosis of the precapillary arteriole. Occasionally the rise will be more than 13 mm. of mercury, but in the previous report<sup>3</sup> this was only seen in subjects with hypertension and was thought to indicate a considerable degree of spasm of the precapillary arteriole.

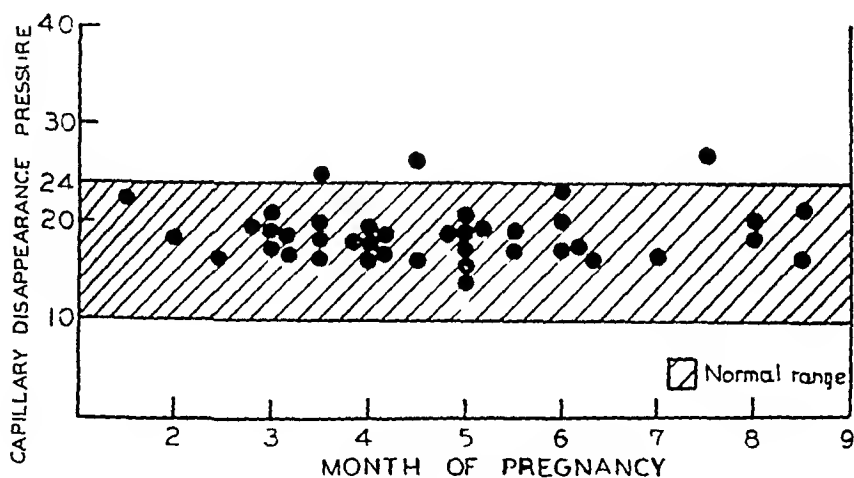


Fig. 3.—Showing the range of capillary disappearance pressure in women at various months of pregnancy. The "normal range" is taken from the nonhypertensive subjects shown in Fig. 2.

Capillary disappearance pressure was measured in a series of pregnant women, and the results are shown in Fig. 3. The systolic blood pressure in every case was below 140 mm. of mercury. Only 3 subjects had a trifling elevation of capillary disappearance pressure, never exceeding 28 mm. of mercury. The average capillary disappearance pressure was 18.5, as compared to 17 for the nonpregnant group. As the deviation from the mean is essentially the same in the two groups, the slight elevation seen in an occasional pregnant subject could have been anticipated.

The increase in pressure after histamine is shown in Fig. 1. While most of the women showed a rise of pressure within the normal limits, it is seen that 7 showed a rise of less than 3 mm. of mercury and 5 a rise of more than 13 mm. of mercury. The latter finding was the more unexpected of the two, suggesting as it did some degree of arteriolar spasm.

### III. Cutaneous Lymphatic Flow

The method has been described elsewhere.<sup>4-5</sup> Approximately 0.03 c.c. of patent blue, prepared according to the directions of McMaster,<sup>4</sup> is injected intracutaneously in the flexor surface of the forearm, and its spread noted over a period of 20 minutes. Results are expressed as normal and increased.

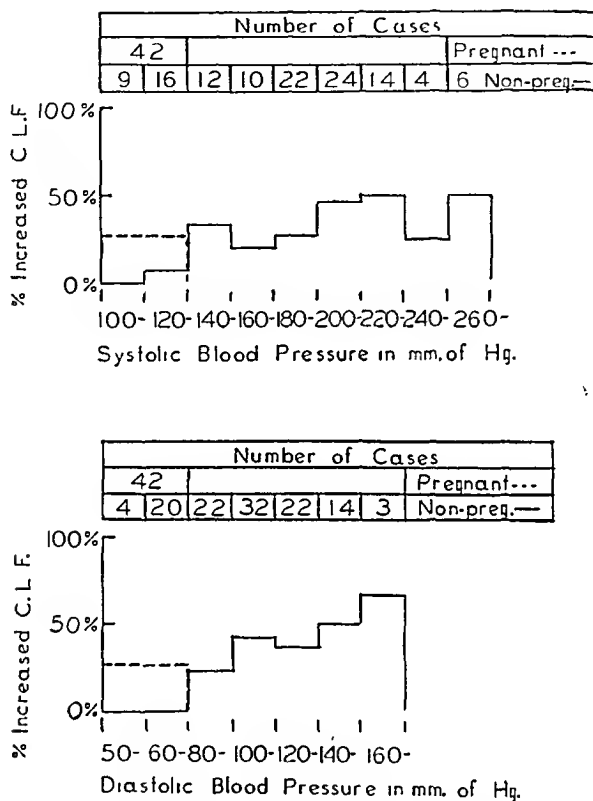


Fig. 4.—Showing the frequency of increased cutaneous lymphatic flow at various levels of systolic and diastolic blood pressure in pregnant and nonpregnant subjects.

The relationship between cutaneous lymphatic flow and systolic and diastolic blood pressure in pregnant and nonpregnant subjects is shown in Fig. 4. It is apparent that in nonpregnant subjects with systolic pressure below 140, increased lymphatic flow occurred in only 4 per cent of the subjects, while in the corresponding pregnant group it was increased in 26 per cent. No nonpregnant subjects with diastolic pressure below 80 showed increased cutaneous lymphatic flow, as compared with 26 per cent of the pregnant subjects.

The relationship between cutaneous lymphatic flow and capillary disappearance pressure in pregnant and nonpregnant subjects is shown in Fig. 5. Here, there is a suggestion that increased cutaneous lymphatic flow, both in pregnant and nonpregnant subjects, is apt to be associated with the higher measurements of capillary disappearance pressure. Considering only those persons with capillary disappearance pressure of 30

mm. of mercury or lower, cutaneous lymphatic flow is increased in 26 per cent of the pregnant subjects and in 19 per cent of the nonpregnant subjects; a difference not significant.

The occurrence of increased cutaneous lymphatic flow, normal blood pressure and normal capillary disappearance pressure, has been observed in a small group of cases included in a report by Pendergrass, Hodes

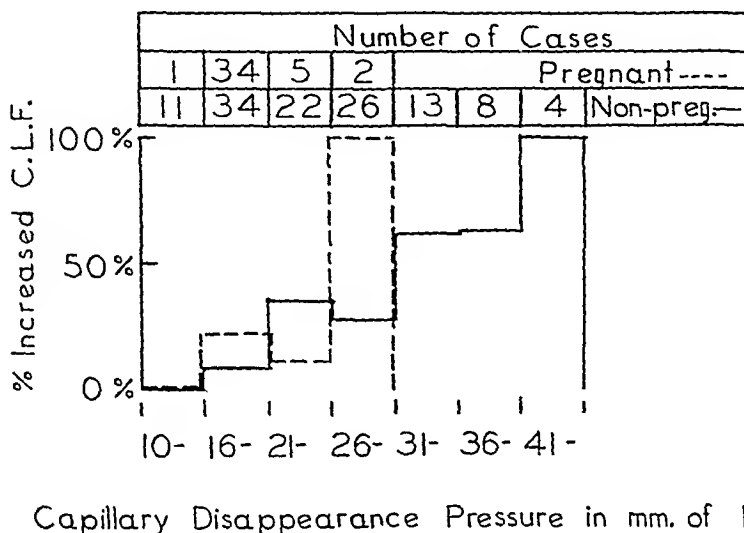


Fig. 5.—Showing the frequency of increased cutaneous lymphatic flow at various levels of capillary disappearance pressure in pregnant and nonpregnant subjects.

and Griffith.<sup>6</sup> These persons all had edema without evidence of heart or kidney failure or hypoproteinemia. This edema tended to be eyelid and, in women, was frequently associated with the menses. The sera of these persons was able to inhibit the normal water diuresis of rats, and they usually improved or recovered after pituitary irradiation. No such subjects were included in the "nonpregnant" series here reported, which is made up of normal subjects or persons normal except for the presence of a hypertension with its associated phenomena.

### Discussion

Increased cutaneous lymphatic flow can, in all probability, be accepted as evidence of increased loss of fluid from the capillaries. This has been discussed previously.<sup>5</sup> Such increased loss of fluid might result from: (1) Increased capillary pressure. (2) Diminished colloid osmotic pressure. (3) Increased capillary permeability.

The evidence presented by others, especially Dieckmann,<sup>7</sup> seems to rule out a hypoproteinemia as an etiologic factor. While such measurements were not made in our entire series they were made in 10 cases, and in these there was no evidence that a lowered plasma protein was a factor in the increased cutaneous flow.

Another alternative is that an elevated capillary pressure may be the cause of an increased flow of fluid from the capillaries. This suggestion



requires repetition and elaboration of certain hypotheses previously presented by Griffith, Rutherford, Roberts and Lindauer.<sup>8</sup>

It is probable that rise of intracapillary pressure tends to be limited by a dynamic equilibrium in which outflow from the capillary occurs not only into the vein but also through the capillary wall. The latter phenomenon is, however, limited in rate by the tendency of the colloid osmotic pressure in the capillary to rise as the residual protein becomes concentrated. When fluid is rapidly being lost from the capillaries, as in the first stage of shock, an early physiologic response is an arteriolar constriction which actually lowers capillary pressure and tends to prevent further loss of fluid. This, in general, has been pointed out by Moon.<sup>9</sup>

The gradient of pressure as one passes from large artery to capillary varies with the freedom of flow at each point in the progression. If capillary disappearance pressure is actually, as we think, a measure of pressure in the precapillary arteriole, it may at times be high as the result of arteriolar hypertension, either with or without rapid fall of pressure between the point of measurement and the capillary, depending upon the state of arteriolar tone between the point of measurement and the capillary, and hence with or without a tendency to increased cutaneous lymphatic flow; and impeded flow beyond the capillary may cause rise of capillary pressure with increased lymphatic flow without elevation of pressure so far back as the point at which capillary disappearance pressure is measured. A tendency to correlation between capillary disappearance pressure and cutaneous lymphatic flow would, therefore, be expected, but not perfect correlation.

In Fig. 2 it was shown that in persons with normal blood pressure average capillary disappearance pressure is 17 mm. of mercury. In Fig. 5 it is seen that cutaneous lymphatic flow is not increased, either in pregnant or nonpregnant subjects, until the capillary disappearance pressure exceeds 16 mm. of mercury. By comparison with Fig. 4, it is seen that increased cutaneous lymphatic flow practically does not occur at systolic pressure below 140 and diastolic pressure below 80. Therefore, one may say that in hypertensive subjects as well as in pregnant women increased cutaneous lymphatic flow may occur while capillary disappearance pressure is within the upper half of the normal range, but that the likelihood of its occurrence increases with the rise of the capillary disappearance pressure. Thus it seems most likely that the increased loss of fluid from the capillaries in certain pregnant women is due to a slight increase in capillary pressure.

This evidence has no bearing upon the possibility of a primary increase in capillary permeability.

### Summary

Capillary counts before and after histamine, capillary disappearance pressure before and after histamine, and cutaneous lymphatic flow were

measured in a series of women in normal pregnancy, and the results compared with those obtained in normal and hypertensive subjects. All capillary studies tended to be normal, except that occasionally in a pregnant woman the rise in capillary disappearance pressure after histamine was somewhat excessive. Cutaneous lymphatic flow was found to be increased in pregnant subjects when compared with others with corresponding blood pressure, and this showed a rough correlation with the level of capillary disappearance pressure. Theoretical considerations are discussed and the conclusions reached that the increased cutaneous lymphatic flow is most probably due to a slight rise in capillary pressure.

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## ENDOMETRIOSIS INTERSTITIALE, WITH A REPORT OF THREE CASES\*

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IN 1937 J. R. Goodall<sup>1, 2</sup> focused attention on a group of uterine tumors which he considered a type of endometriosis in which the stromal cells predominated to the exclusion of the glandular elements. He designated this condition as *endometriosis interstitiale*. The tumors occurred either in the form of a diffuse infiltrative process, or as a circumscribed mass resembling a soft fibroid. Microscopically, they were characterized by an abundant proliferation of a spindle-cell stroma containing numerous thick-walled blood vessels of muscular type. The first case to be reported in the literature was by Casler<sup>3</sup> and appeared in 1920. Three instances were also reported by Frank<sup>4</sup> in 1932.

The present paper deals with three similar cases which were observed in the Hartford Hospital during the past two years. The frequency of occurrence of this lesion obviously cannot be indicated from the available literature. However, the following figures give some idea of the activity of the Hartford Hospital in this field. During the years 1940, 1941, and 1942, seven hundred fibroid uteri were examined in the laboratory, while in the same interval a gross diagnosis of endometriosis was made at operation in 179 cases with microscopic confirmation in 90. Since other reports have indicated that these tumors have been mistakenly classified as myosarcomas, a review of the sarcomas of uteri at the Hartford Hospital was made but failed to reveal any additional instances of stromal-cell endometriosis.

The present report seems warranted because of the apparent rarity of the condition and to emphasize the anatomic features which establish the correct diagnosis.

CASE 1.—(H. H. 426-676.†) J. M., a 22-year-old single, American girl, was admitted to the ward service of the Hartford Hospital on February 2, 1942 with a diagnosis of incomplete abortion. She had missed her period in November but menstruated again in December and January. The last period occurred a week later than expected and was accompanied by unusual cramps in the lower abdomen. Following this period, she continued to spot until her admission two weeks later. She had experienced no fever and denied instrumentation. Her past history was not contributory. On February 7, a curettage was done. The uterus was enlarged, globular, smooth, freely movable, and lying in an anterior position. No masses were found in the adnexal or parametrial regions. The cervix was firm. The uterine sound entered the cavity a

\*Read at a meeting of the New York Obstetrical Society, December 14, 1943.

†Reported by Dr. Louis Middlebrook, *Connecticut S. M. J.* 7: 544, 1943.

distance of 7.5 cm. After dilatation the cavity was explored with an ovum forceps. No tissue was obtained at first, but finally, a portion of a firm smooth mass (specimen I) was removed with a sponge forceps. The patient was discharged from the hospital a few days later. The tissue removed was examined and a diagnosis of endometriosis interstitialis was made.

The patient was readmitted February 16, and the entire uterus and both tubes removed (specimen II). (Fig. 1.) The ovaries appeared normal and contained numerous follicular cysts. There were no adhesions or enlarged glands. She was discharged on the twenty-first hospital day.

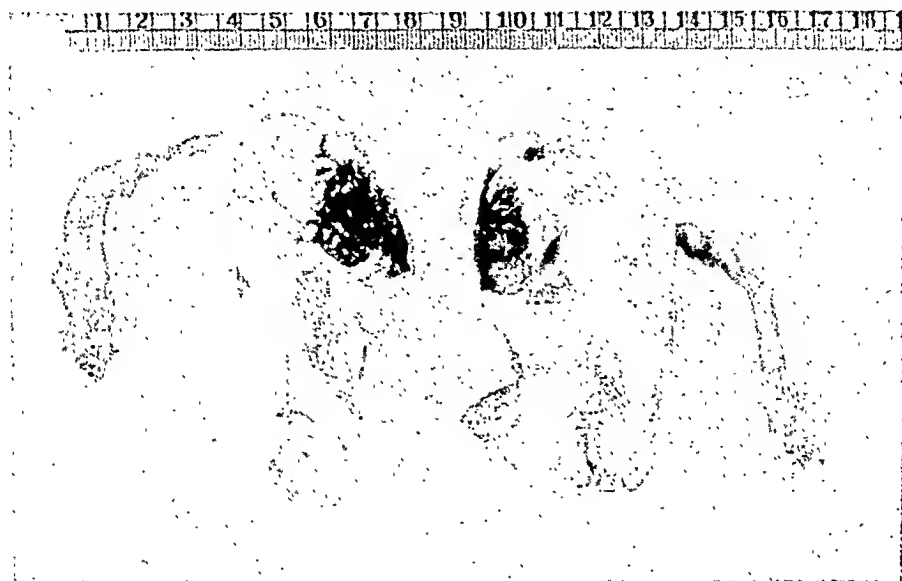


Fig. 1. Case 1.—Uterus opened showing polypoid tumor mass in fundus.

*Pathological Report.* Specimen I.—*Gross:* The specimen was a polypoid mass of firm gray tissue which measured 2.5 by 1 by 1 cm. The surface had a hemorrhagic appearance.

*Microscopic:* Sections showed a tumor composed of delicate spindle-shaped cells arranged in interlacing strands. The cells had deep blue vesicular nuclei and showed occasional mitoses. In some portions, the cells were closely packed, but in other parts were separated in a coarse reticulated pattern. There were many thin-walled dilated vascular channels in these regions which suggested lymphatic structures. A more striking feature was the presence of numerous thick-walled blood vessels of arterial type which were found in the more cellular portions of the tumor (Fig. 2). The arrangement of these vessels in groups resembled the spiral arteries of the endometrium. No glandular elements were present. Silver stains for reticulum showed a network of fibers which formed a basket-weave pattern about the individual cells. This arrangement resembled that of the stroma of the normal endometrium. A diagnosis of endometriosis interstitialis was made.

*Specimen II.*—*Gross:* The specimen consisted of uterus with cervix and tubes attached. The uterus which was slightly asymmetric and enlarged, measured 10 by 5.5 by 3.5 cm. The cervix was small, the os was round, and the endocervix was lined by a smooth pale mucous

membrane. When the uterus was opened, a pedunculated soft red-brown mass was found projecting into the uterine cavity from the fundus (Fig. 1). This papillary mass measured 4 cm. in length. Its cut surface was a soft pale pink. The tumor extended into the myometrium at the point of attachment although the boundary between the tumor and myometrium was sharp.

At one point an isolated tongue of tumor tissue projected above the cut surface of the myometrium beyond the line of attachment of the main mass of tumor. This appeared to project from a dilated vascular channel into which it had grown. The tip of the polypoid mass was hemorrhagic and ulcerated. The endometrium in other portions of the uterine cavity was pale and atrophic. The Fallopian tubes were normal.

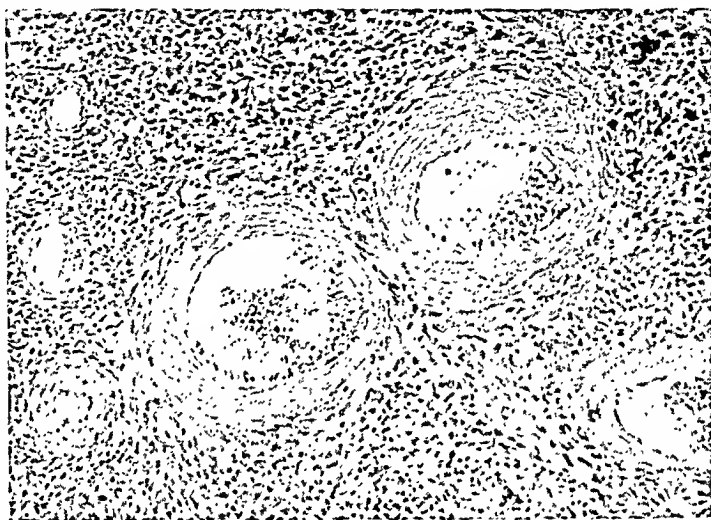


Fig. 2. Case 1.—Cellular spindle-cell stroma with thick-walled blood vessels. H. & E. ( $\times 180$ ).

*Microscopic:* The tumor presented histologic features which were identical with those of the previous biopsy specimen. There was a sharp line of demarcation between myometrium and the tumor. At one point a tongue-like growth of tumor projected into a dilated vascular channel. It was covered by flattened endothelium which was invaginated by the tumor growth into the vessel's lumen.

*Comment:* The gross and histologic appearance of this tumor was that of a neoplasm of low malignancy arising from endometrial stroma. The anatomic features were identical with those described by Goodall and others as endometriosis interstitialis. The patient although retaining both ovaries was well and free of signs or symptoms referable to the pelvis when last seen in September, 1943. She stated that her breasts reacted each month with swelling and tenderness as they had formerly at each period.

CASE 2.—(H. H. 453-891.) E. M., a 43-year-old white, American housewife, was first admitted to the Hartford Hospital on March 6, 1943. She had been married many years but never pregnant. She had begun to menstruate irregularly fifteen months before admission, though her periods up to that time had been regular with moderate dysmenorrhea. She flowed constantly from January to June, 1942 when she had three sudden hemorrhages of bright red blood and clots. In June, 1942 she was operated on in another hospital and a mass which was thought to be

a cervical fibroid (specimen I) was removed. A pathologic diagnosis of submucoid leiomyoma was made.

After this operation her periods became regular but more prolonged than usual until two months before admission when she again began to bleed constantly. She was referred for hysterectomy by the family physician. Examination upon admission revealed the presence of a black necrotic mass 6 cm. in diameter, lying in the vagina and apparently the cause of a foul, dark, bloody discharge. This mass was attached by a long, fairly firm pedicle to the upper part of the uterine cavity. Hysterectomy was considered unwise in the face of the apparent uterine infection, so under anesthesia the mass was removed with



Fig. 3. Case 2.—Structure of tumor removed at first operation (specimen I). H. & E. ( $\times 180$ ).

the aid of long curved seissors. The mass resembled necrotic products of conception (specimen II). The uterus was packed with gauze containing sulfanilamide crystals, after removal of which, the patient was permitted to go home. Histologic examination of the tissue showed typical stromal-cell endometriosis. She was readmitted on April 6, and the fundus of uterus, tubes, and ovaries were removed, (specimen III). A total hysterectomy had been contemplated but because the patient weighed 210 pounds, had hypertensive heart disease with blood pressure of 240/130 and a cervix which was deeply and firmly held in the pelvis, the less radical procedure was carried out.

*Pathological Report. Specimen I.—Gross:* The specimen was an irregularly spherical mass 5 cm. in diameter having a hemorrhagic ulcerated surface. The cut surface was composed of soft yellow-pink tissue with numerous cystic zones containing gelatinous material.

*Microscopic:* The tumor was made up of delicate spindle-shaped cells arranged in an interlacing pattern. Occasional cells showed mitosis. Some thick-walled muscular vessels were present (Fig. 3). Surface of tumor was ulcerated and showed acute inflammatory infiltration.

*Comment:* This was considered to be an ulcerating submucous fibromyoma of increased cellularity and mitotic activity.

*Specimen II.—Gross:* The specimen consisted of a mass of blood clot containing several fragments of gray tissue.

*Microscopic:* Sections revealed a cellular tissue composed of delicate spindle-shaped cells with clusters of thick-walled muscular vessels of arterial type dispersed throughout. The cells resembled those of the endometrial stroma although no glandular elements could be found. They showed frequent mitoses. The surface of the mass was covered by a flattened layer of columnar epithelium. This gave the tissue a polypoid appearance.

*Comment:* A diagnosis of endometriosis interstitialis was made.

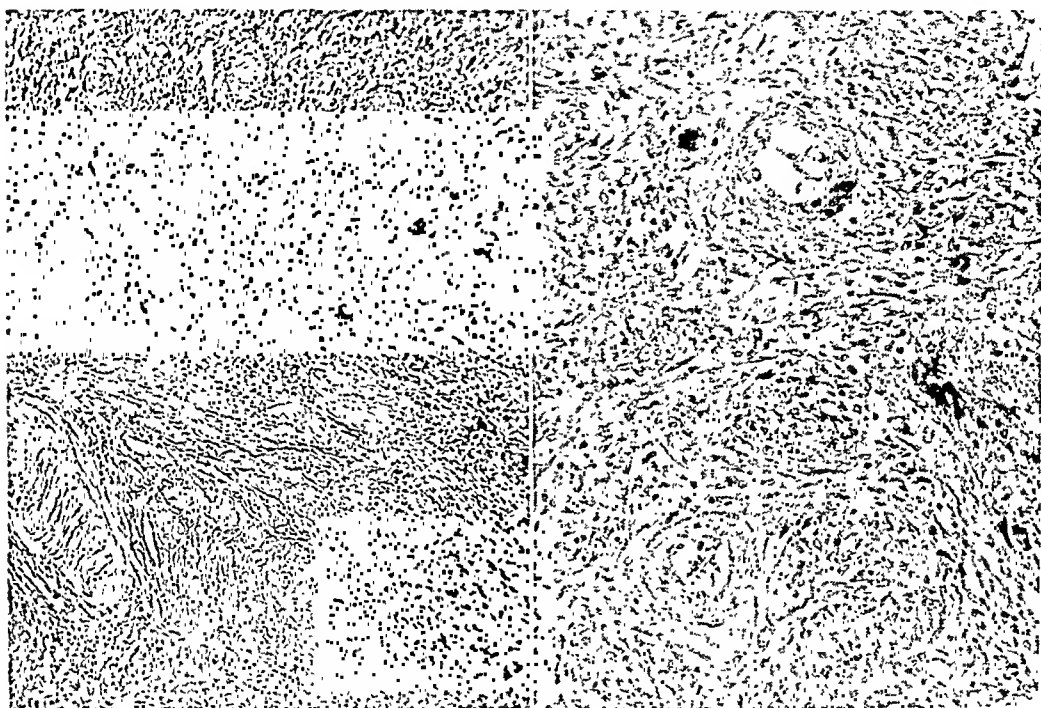


Fig. 4.

Fig. 5.

Fig. 4. Case 2.—Uterus sectioned showing multilocular cystic tumor of myometrium.

Fig. 5. Case 2.—Showing tumor above and myometrium below with indefinite boundary. Cellular stroma with thick-walled vessels are prominent. H. & E. ( $\times 80$ ).

*Specimen III.—Gross:* The specimen was a supracervical uterus with one tube and ovary. The uterus measured 10 cm. in greatest diameter and was distorted by several small myomatous nodules. On cross section of uterus a sharply circumscribed multilocular cystic tumor 5 cm. in diameter was found in the fundic portion of the myometrium (Fig. 4). This mass had a variegated red and yellow appearance. The cystic spaces contained clear yellow fluid and had delicate walls. The tumor extended to the endometrial lining but there were no polypoid projections into the small uterine cavity. The endometrial lining had a granular red appearance. Several myomatous nodules from 1 to 3 cm. in diameter were also present within the myometrium. The tubes and ovaries had a normal appearance. The ovaries contained simple and follicular cysts.

*Microscopic:* Histologic sections of the tumor showed masses of small spindle cells resembling endometrial stroma scattered throughout which were clusters of thick-walled blood vessels of arterial type (Fig. 5). The

tumor cells showed rare mitoses. The cystic spaces had a flattened endothelial lining and suggested dilated vascular channels. The tumor infiltrated the adjacent myometrium to some extent, but this was not marked. Silver stains revealed a basket-weave pattern as seen in the first case.

*Comment:* Review of the three specimens from this case showed that the initial specimen had features similar to the latter two. A silver stain to demonstrate the basket-weave pattern of the reticular network would have aided in establishing the diagnosis at the time of the first biopsy.

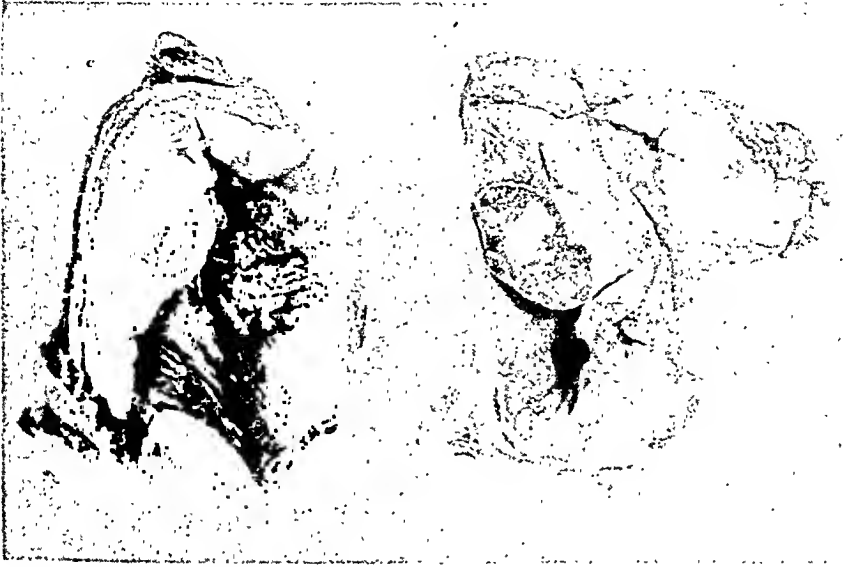


Fig. 6. Case 3.—Section of uterus through large cystic cavity in myometrium.

CASE 3.—(H. H. 455-563.) M. A., a 57-year-old single, white American schoolteacher, was admitted to Hartford Hospital March 25, 1943. Her menopause had occurred at the age of 50 without incident or history of previous menstrual difficulty. She had noted a gradual enlargement of the abdomen during the past six months but thought nothing of this until she began to have abdominal pain and a rapid enlargement of the mass in the lower abdomen during the past two months. She had lost 15 pounds and had been treated for pleurisy two months previously. Examination showed a symmetric, easily movable mass occupying the upper part of the true pelvis, rising to the umbilicus. It felt solid. The introitus was virginal. Remainder of the physical examination revealed nothing of note.

Stereoscopic x-rays of the thorax showed only slight pleural thickening at both bases. Exploratory laparotomy was done with the tentative diagnosis of fibroid of the uterus and possible carcinoma of the ovaries. At operation the upper abdomen was found to be the seat of a large neoplastic mass which was apparently primary in the gall-bladder, with metastases in the omentum, preaortic glands, liver, and peritoneum. The complete excision of the uterus, tubes and ovaries was easily carried out.

The patient left the hospital after an uneventful primary recovery, but died two months later at her home from extensive carcinomatosis.

*Pathological Report.*—*Specimen I. Gross:* The specimen consisted of uterus with cervix, tubes and ovaries attached. The uterus was irregularly spherical in shape and measured 15 cm. in diameter. On



its serosal surface, there were several plaque-like thickenings each 1 cm. in diameter. These were implants of metastatic squamous-cell carcinoma which were similar to those found elsewhere in the peritoneum at the time of operation. When the uterus was sectioned a large cystic cavity was entered; this contained approximately 500 c.c. of brown blood-tinged fluid in which many cholesterol crystals floated (Fig. 6).

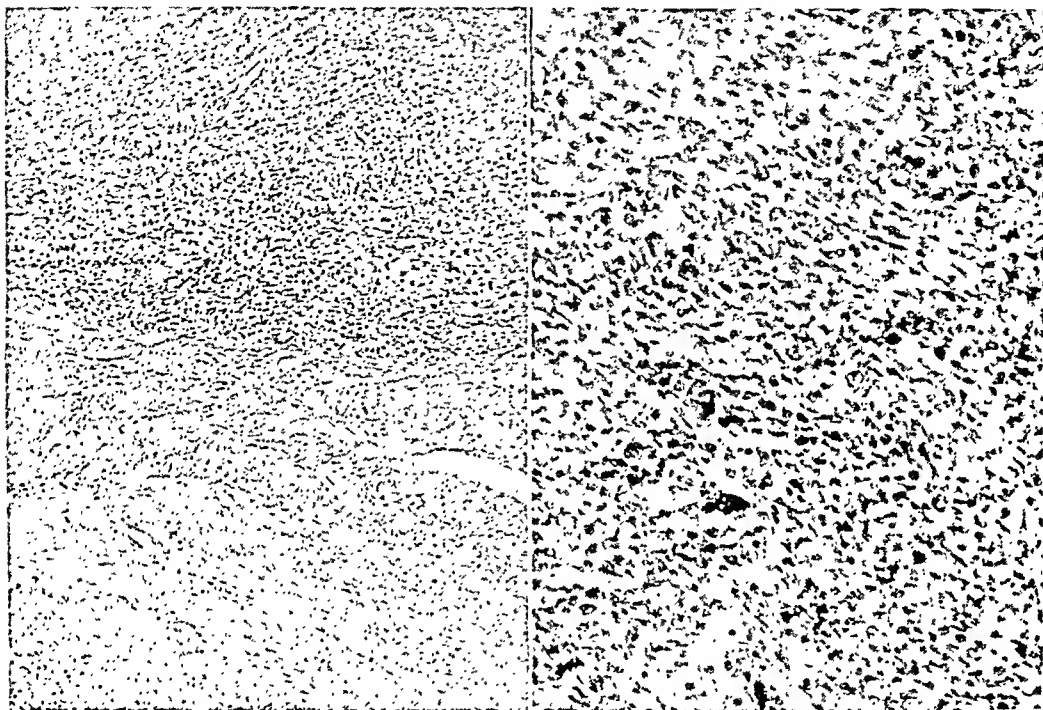


Fig. 7.

Fig. 8.

Fig. 7. Case 3.—Shows spindle-cell lining with junction with myomatous portion of tumor H. & E. ( $\times 110$ ).

Fig. 8. Case 3.—High power of inner cellular zone. H. & E. ( $\times 330$ ).

The lining of the cyst was red-brown and smooth, and in one region a yellow-green irregular mass 7 cm. in diameter projected from the wall into the cavity. The mass was composed of soft, friable tissue and beneath it there was a layer of hemorrhagic tissue 5 cm. in diameter in which no structural detail could be made out. Surrounding the inner layer there was a 1.5 cm. layer which had the gross appearance of a fibroid and which formed a sharp boundary between the tumor and the adjacent myometrium. The endometrial cavity which was elongated and flattened by the cystic mass had no communication with the cyst. The endometrial lining was pale and atrophic. The cervix and tubes were normal. The ovaries were atrophic.

*Microscopic:* Microscopic sections showed the cyst lining made up of a thick layer of small spindle-shaped cells forming a reticulated pattern. Surrounding this were interlacing bundles of fibromuscular tissue typical of a myoma with a sharp demarcation between this portion and the adjacent myometrium. The inner zone resembled endometrial stroma but no glandular elements could be found (Figs. 7, 8). Silver stains showed a basket-weave pattern similar to normal endometrium. This contrasted strikingly with the myomatous outer portion

which showed the reticulum arranged in parallel strands as in normal myometrium.

*Comment:* This case appeared to represent a stromal endometriosis which was associated with myoma formation comparable to an adenomyoma but without the glandular elements of the endometrium participating in the process. The metastatic squamous cell carcinoma was unrelated to the uterine condition but resulted in the patient's demise.

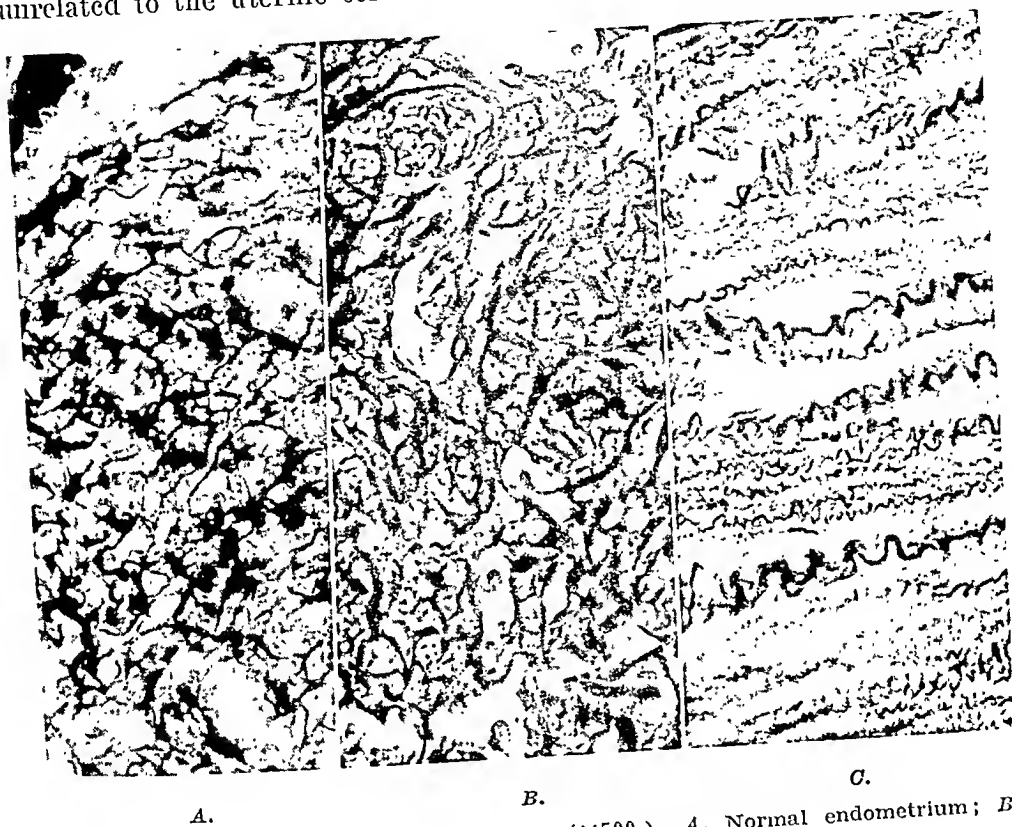


Fig. 9.—Bielschowsky stain for reticulum. ( $\times 500$ .) A, Normal endometrium; B, endometriosis interstitiale; C, myometrium.

### Discussion

The present cases all showed lesions of a circumscribed type. The first was a soft, polypoid mass resembling a submucous fibroid tumor and similar to several others reported in the literature. The other two showed cystic changes which have not been found as a feature of the previously recorded cases. In the second case these spaces had a microscopic appearance which suggested dilated vascular channels. They may have arisen from the abundant vascular component which is a prominent characteristic of these tumors.

Infiltration of the myometrium was not extensive in any of these instances nor was there evidence of anaplasia of the cells or other changes indicative of malignancy. However, as pointed out in Goodall's monograph<sup>5</sup> and the reports of Robertson et al.,<sup>6</sup> the disease may pursue a variable course. In some instances the process has assumed a malignant character uncontrolled by operation, ultimately becoming refrac-

tory to irradiation and ending in extensive infiltration of the pelvic tissue which has led to death by obstruction of the ureters. On the other hand, it is essential to differentiate this process from the leiomyosarcomas with their attendant high mortality from extensive metastatic disease. This is especially true in the infiltrative types of stromal endometriosis which have extended into the parametrial tissue where sterilization is of value in retarding the process as in the usual varieties of endometriosis.

The employment of silver stains to show the reticulum pattern as demonstrated by Frank<sup>4</sup> and emphasized by Feinberg<sup>7</sup> and Robertson<sup>6</sup> has proved of especial value. The typical basket-weave pattern of the reticulum of the normal endometrium was well preserved in all three of the present tumors and contrasted distinctly with the arrangement of the reticulum in parallel strands in myomatous tumors (Figs. 9a, b, c). In the second case, the use of the silver stain on the specimen from the first operation would have assisted in establishing the correct diagnosis earlier.

The third case with the combined myoma and endometriosis interstitiale is noteworthy. A diffuse type of process resembling adenomyosis without glandular elements has been reported by Robertson,<sup>6</sup> Casler,<sup>3</sup> and Frank.<sup>4</sup> In the present instance the possibility that this was originally a circumscribed adenomyoma with glandular elements must be considered, since the patient was seven years past the menopause and atrophy of the glandular components may have occurred.

### Summary

Three cases of endometriosis interstitiale of uterus are reported. A feature of two, which has not been previously reported, was the presence of cystic spaces throughout the tumor. The value of silver reticulum stains as an aid in the differentiation from myomatous tumors is emphasized.

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### Discussion

DR. ROBERT T. FRANK.—While the cases shown by Dr. Miller correspond to those reported by Casler and Goodall, they differ from those that I reported, as well as those of Robertson, Hunter, Larson and Snyder.

The main features of the three cases which I described are the elevated, yellowish, 'rubbery' areas appearing between coarse fibrous bands on gross cross section of the uterus. Microscopically, these yellowish areas consist of cells which are not

fully characteristic either of endometrial stroma or of endothelial cells. The main microscopic characteristic in my tumors is the distribution within the lymphatic channels, but almost always covered by intact lymphatic endothelium. Clinically, the process is characterized by slow, persistent growth, a long latent period before recurrence. In my first case, the latency persisted for nine years. Therefore, Robertson's deductions, based on cases with a shorter period of observation, are as yet inconclusive.

In summary, I would say that there exists the typical endometriosis in which both glandular and stromal elements are almost equal in number. Then there are cases with a gradual diminution of the glandular elements until stroma far predominates, and finally, but less easily classifiable, cases probably of different etiology, as described by Dr. Robertson and myself.

DR. G. L. MOENCH.—I was very much interested in the cases presented by Dr. Miller. "Stromal Endometriosis" is certainly rare. When we consider that there is no basement membrane between the endometrium and myometrium it would seem as if both glands and stroma, or either one alone, might easily be misplaced into the muscle tissue. Perhaps, however, the fact that the epithelium determines its stroma and that epithelium may come directly from stromal cells, leads in nearly all cases to an intimate association of glands and stroma. Only under peculiar circumstances does stromal tissue continue to exist alone.

Dr. Miller has suggested that perhaps the glands have degenerated. I might add that perhaps they have not yet formed, or we might be dealing with embryologically misplaced tissue similar to a tumor I saw in the broad ligament, which was not connected with the tube or uterus and was made up almost entirely of endometrial stroma. This tumor was about the size of a lemon, was removed at the time of a cesarean section, and showed marked decidual reaction.

When we consider all the vagaries of endometriosis, or adenomyosis, as I prefer to call it, it need not strike us as strange that unusual pictures are encountered at times. One fact, however, stands out in the literature and that is that adenomyosis is practically never malignant. Why then "stromal endometriosis" should show such malignant tendencies is not at all clear. There must be some other factor we have not yet grasped and in this light I am not willing to say that Dr. Miller's cases should be interpreted only as "stromal endometriosis."

DR. JOE V. MEIGS (by invitation).—In going over our uterine tumors at the Massachusetts General Hospital, we found only one case of the type under discussion. This resembled Dr. Frank's cases more than those of Dr. Miller. This patient was about 36 years of age. She had a total hysterectomy done for what was thought to be sarcoma. In going over the slides, we found worm-like areas infiltrating the lymphatics into the broad ligaments and the uterine wall. The patient was alive ten years after operation. When Dr. Goodall wrote his paper I mentioned this patient to him and he sent me an early copy of his report on this subject. Our pathologist agreed that it probably was a sort of endometrial stromal tumor.

DR. TENNANT (closing).—When we first saw the material from the first case we thought we were dealing with a sarcoma probably arising from the myometrium, but we were impressed by the numerous thick-walled blood vessels present in this case and also in our subsequent cases. These findings have been emphasized by Robertson in his paper as a characteristic of stromal-cell endometriosis.

The other point of value to us in differentiating this tumor from the myosarcomatous tumors was the silver reticulum stain which in the three cases showed a distinct basket-weave pattern quite different from the pattern in the myometrial tumors.

## THE ELDERLY PRIMIPARA\*

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SINCE the publication in 1938<sup>1</sup> of a study of 240 cases of elderly primiparas delivered in the Woman's Clinic of the New York Hospital, many more cases have occurred on this service and more data have been collected on this obstetrical problem. The following study is based on an exhaustive review of 830 elderly primiparas delivered during the eleven-year period from September 1, 1932, to September 1, 1943, and thus includes the 240 cases originally presented. During this period of time there have been 30,880 full-term and premature deliveries in this clinic. Of this number 830 were elderly primiparas, an incidence of 2.68 per cent. An elderly primipara is any patient thirty-five years of age or over delivered for the first time of a viable infant.

In this study 424 patients, or 51.1 per cent of the total cases, were 35 to 36 years of age. There were 104 patients, or 12.5 per cent of the cases, 40 years of age or over. The oldest patient in this group was 46 years of age. There were 27 colored patients in the series, an incidence of 3.3 per cent as compared with 4.9 per cent, the incidence of colored patients in the clinic as a whole. Of the total 830 cases, 342 (41.2 per cent) were private patients. This is in distinct contrast to the higher figure of 91.5 per cent as reported by Erving and Power.<sup>2</sup>

In this total group of elderly primiparas, 604 (72.8 per cent) were primigravidas. In the remaining 226 primiparas, 149 had spontaneous abortions, 71 had induced abortions, and 6 had ectopic pregnancies. There was a total of 372 pregnancies in this group, one patient having had 8 spontaneous abortions, and another 7 induced abortions.

It has been stated in the literature<sup>3</sup> that the longer the period of relative sterility (or infertility), the more difficult the labor, and the more frequent the complication. The factor of sterility or infertility cannot accurately be evaluated since we are unable to determine from the histories studied whether or not contraceptive measures had been employed. Table I shows the results in 207 primigravidas married four years or longer.

Previous to the present admission to the hospital at the time of delivery, 51 patients (6.1 per cent) of the 830 had a major or minor operation for a gynecological condition. Myomectomy had been performed in 13 cases, suspension of the uterus in 9, and a unilateral sal-

\*Presented by invitation, at a meeting of the New York Obstetrical Society, January 11, 1944.

TABLE I. OBSTETRIC RESULTS ACCORDING TO YEARS OF MARRIAGE

DURATION OF MARRIAGE	TOTAL CASES	AVERAGE DURATION LABOR	INCIDENCE OF TYPE OF DELIVERY			MORTALITY	
			SPONTANEOUS	VAGINAL OPERATION	CESAREAN SECTION	INFANT	MATERNAL
4 to 6 years	89	20.28 hours	41.6	42.7	15.7	2.24	
7 to 9 years	62	20.49 hours	45.2	40.3	14.5	8.06	1.61
10 to 12 years	31	17.40 hours	48.4	32.3	19.3	9.67	
13 to 15 years	19	16.28 hours	36.8	36.8	26.4	10.52	
16 to 18 years	5	28.33 hours	20.0	40.0	40.0	20.0	
19 years	1	10.00 hours		100.0			

pingectomy and/or oophorectomy in 26, six of the salpingectomies having been performed for ectopic pregnancies.

In this series of elderly primiparas, the same general complications of pregnancy were encountered as in the clinic as a whole. There were 23 patients (2.7 per cent) with rheumatic heart disease. In a five-year study of all clinic patients the incidence of cardiac disease was 3.5 per cent. Myoma uteri occurred in 49 cases (5.9 per cent), as compared with the incidence of 1.9 per cent for the clinic. The size of the myomas varied from small nodules to large intramural and subserous masses. In only 8 cases, however, was "myoma uteri" the indication for cesarean section. The incidence of toxemia was much higher in the elderly primipara group than in the clinic as a whole, the incidence in the former being 13.98 per cent as compared with 7.29 per cent in the latter. The following table shows the incidence of the types of tox-

TABLE II. TYPES OF TOXEMIA IN THE ELDERLY PRIMIPARAS

TYPE OF TOXEMIA	INCIDENCE IN ELDERLY PRIMIPARAS	INCIDENCE IN TOTAL CLINIC
Mild pre-eclampsia	5.18	3.45
Severe pre-eclampsia	2.65	0.75
Eclampsia	0.62	0.20
Renal disease	0.24	0.26
Hypertensive disease	2.28	1.09
Acute yellow atrophy	0.24	0.01
Unclassified	2.77	1.53
Total	13.98	7.29

emias. A study of all other complications encountered in the elderly primiparas did not show any variation in incidence from that found in the total clinic.

The incidence of contracted pelvis in the clinic as a whole, is 9.2 per cent. In the 830 cases of elderly primiparas 108, or 13.0 per cent, had contracted pelvises. It is stated in the literature<sup>4</sup> that the funnel pelvis is encountered more frequently in the elderly patient. A study of the contracted pelvises in the clinic as a whole showed that the funnel typical pelvis occurred in 28.2 per cent, while in the elderly primipara group it was found in 45.3 per cent of the cases.

Although we have no statistical information available at this time, we feel that x-ray pelvimetry is indicated in all cases of elderly primip-

aras inasmuch as it gives more information about the pelvis than can be obtained through the clinical methods ordinarily employed. We have used a modification of the Caldwell-Moloy technique of x-ray pelvimetry in this clinic during the past few years, and utilized this method in 150 cases of elderly primiparas. The distribution of these cases as to the suggested and ultimate types of delivery was found to be too scattered to yield any statistical conclusions at this time.

It has been the general impression that when the elderly primipara goes beyond the expected date of confinement (E.D.C.), the labor is usually prolonged and a difficult delivery can be expected. The following table shows the time relationship of the day of delivery to the expected date of confinement.

TABLE III. RELATIONSHIP OF EXPECTED DATE TO THE DAY OF DELIVERY

DAY OF DELIVERY	TOTAL CASES	INCIDENCE
15 days or more before E.D.C.	123	14.8
1 to 14 days before E.D.C.	283	34.1
Delivered on E.D.C.	37	4.5
1 to 14 days after E.D.C.	290	34.9
15 days or more after E.D.C.	83	10.0
E.D.C. unknown	14	1.7
Total	830	100.0

It is noted that 10.0 per cent of the patients delivered 15 days or more beyond the expected date, the longest period being 45 days.

The 83 patients that delivered 15 or more days past term have been studied in detail and the results compared with those of the entire group of 830 elderly primiparas as well as with the figures for the clinic as a whole. The results are shown in the following table.

TABLE IV. RESULTS IN PATIENTS DELIVERING 15 DAYS OR MORE BEYOND E.D.C.

	83 CASES	830 CASES	TOTAL CLINIC
Average duration of labor	24.19 hours	20.41 hours	18.00 hours
Incidence of prolonged labor	28.91 %	17.59 %	9.1 %
Incidence of operative delivery	69.87 %	55.54 %	24.3 %
Incidence of cesarean section	15.66 %	13.37 %	2.9 %
Incidence of infantile mortality	24.09 %	7.64 %	3.71 %
Average weight of infant	3,415 Gm.	3,380 Gm.	3,350 Gm.

The definition of prolonged labor in this clinic is a labor lasting 30 hours or more. The longest labor among the 83 cases was 109 hours and 50 minutes, the shortest 2 hours and 20 minutes, as compared to 109 hours and 50 minutes and 1 hour and 45 minutes, respectively, for the total elderly primipara group. The incidences of prolonged labor and infantile mortality were high in this group of patients that delivered 15 or more days past the expected date of delivery. The incidence of infantile mortality in this group of 83 cases was 24.09 per cent; 8.43 per cent occurred in the patients having a labor lasting less than 30 hours, and 15.66 per cent in the prolonged labor group. These factors of increased fetal mortality and prolonged labor would indicate that the

primipara who falls into this classification should be considered for a more radical type of treatment.

In this study of 830 cases, vertex presentation was found to occur in 91.8 per cent of the cases and breech in 7.2 per cent. The incidence of breech presentation in the clinic as a whole is 4.72 per cent. There were 60 cases of primary breech presentation in this study and only 7 were associated with myoma uteri. Of the breech presentations 40 cases (66.6 per cent) were delivered by breech extraction, and 20 cases (33.3 per cent) by cesarean section. The gross infantile mortality rate in the 40 cases of breech extraction was 22.5 per cent as compared to 13.3 per cent in the breech extractions in the total clinic population. In the 20 cases delivered by cesarean section there were no infantile deaths. Another recent paper from this clinic has reviewed in detail 55 cases of primary breech presentations occurring in elderly primiparas.<sup>5</sup> The incidence of posterior position in 762 vertex presentations was 15.2 per cent as compared with 8.7 per cent in the total clinic. On admission to the hospital at the onset of labor 60.7 per cent of the vertex presentations were engaged and 39.3 per cent nonengaged. In a previous report<sup>6</sup> the incidence of nonengagement of the head in a control series of patients was 20.9 per cent. The incidence of operative delivery was 59.9 per cent in the group of elderly primiparas when the head was not engaged at the onset of labor, and the incidence of cesarean section was 22.6 per cent.

The incidence of premature rupture of the membranes in this study was 36.1 per cent, which figure is the same as that for the total clinic population. The definition of premature rupture of membranes in this clinic is rupture of the membranes before or coincident with the onset of labor. There were 7 patients who developed an intrapartum infection, and six of these occurred in the prolonged labor group. The membranes had ruptured prematurely in three of these cases. When the labor is prolonged, the incidence of puerperal infection and infantile mortality increases. The following table shows these incidences.

TABLE V. EFFECT OF PROLONGED LABOR

DURATION OF LABOR	INCIDENCE OF INFECTION		INCIDENCE OF INFANT MORTALITY
	INTRAPARTUM	PUERPERAL	
1 to 29 hours	0.2	5.6	4.3
30 hours or more	4.1	19.8	13.0

The type of delivery in the elderly primipara is one of the most important problems that confronts the obstetrician. Table VI shows the types of delivery employed in this clinic, and compares the incidence with those occurring in the clinic as a whole.

From this table it is seen that the incidence of operative delivery is 55.5 per cent as compared to 24.34 per cent for the total clinic. Piper forceps on the aftercoming head were employed in 5 cases of breech



TABLE VI. TYPE OF DELIVERY

TYPE OF DELIVERY	INCIDENCE	
	ELDERLY PRIMIPARA	TOTAL CLINIC
Spontaneous	44.5	75.66
Forceps: low	24.7	12.19
mid	11.4	3.82
high	0.2	0.02
Breech extraction	4.8	4.08
Version and extraction	0.5	0.45
Craniotomy	0.5	0.15
Cesarean section	13.4	2.91
Other types	0.0	0.72

extraction, Dührssen's incisions were performed in 10 cases and manual removal of the normally implanted placenta was done in 11 cases (1.5 per cent as compared to 0.6 per cent for manual removal in the total clinic). There were 3 instances in which forceps delivery was attempted and failed; two of these cases were delivered by version and extraction, and in the other a craniotomy had to be performed. There were 97 patients who received a medical induction either to stimulate or initiate labor. Thirty-five of these received intranasal pituitrin (pitocin). Of the 97 patients 41 delivered spontaneously, 56 had operative deliveries, and there were 15 infantile deaths. The medical induction was successful in 53 cases. A Voorhees bag was used in 6 cases, and a Wales bougie in one case.

There were 111 cesarean sections in this group of 830 elderly primiparas, an incidence of 13.4 per cent. The types of cesarean sections employed are shown in the following table.

TABLE VII. TYPE OF CESAREAN SECTION

TYPE	CASES	INCIDENCE
Classical	37	33.3
Low cervical	64	57.7
Radical	7	6.3
Ricci	1	0.9
Waters	1	0.9
Latzko	1	0.9
Total	111	100.0

Following the cesarean section, myomectomy was performed in five patients in whom the indication for the operation was not myoma uteri. Hysterectomy was performed in seven instances, five because of myoma uteri, one because of an abnormality of the uterus (uterus didelphys), and one because of failure of the uterus to contract following the removal of the placenta with an associated hemorrhage. Table VIII shows the indications for the cesarean sections.

In the 111 patients who had cesarean sections, 68 (61.2 per cent) had no labor before the operation was performed. In this group there was only one infantile death. The infant, which was premature, died on the thirty-second day of life from an infection of the umbilicus. There were three maternal deaths due to generalized peritonitis. In the cesarean

TABLE VIII. INDICATION FOR CESAREAN SECTION

INDICATION	NUMBER OF CASES
Contracted pelvis	18
Cephalopelvic disproportion	20
Elderly primipara	6
Breech presentation	8
Presentation (2 transverse, 1 compound)	3
Ruptured membranes (6 no labor, 2 no progress with labor)	8
No progress after a trial of labor	8
Cervical dystocia	5
Myoma (7 fundal, 1 cervical)	8
Previous myomectomy	1
Ovarian cyst	1
Toxemia (6 pre-eclampsia, 4 hypertensive, 2 unclassified)	12
Eclampsia	1
Acute yellow atrophy	2
Placenta previa	5
Premature separation of the placenta	3
Cardiac disease	1
Pott's disease	1
Total	111

section group of 43 cases in which there had been some labor preceding the operation, there were three infantile deaths, one from multiple congenital anomalies not compatible with life, and two neonatal deaths from pulmonary atelectasis. There were two maternal deaths in this group. These findings are presented in the following table.

TABLE IX. INFECTION AND MORTALITY RATES IN CESAREAN SECTION

	TOTAL CASES	INCIDENCE		
		PUERPERAL INFECTION	MORTALITY	
			INFANTILE	MATERNAL
Without labor	68	29.4	1.5	4.4
With labor	43	39.5	6.9	4.6
Total sections	111	33.3	3.6	4.5

The following table shows the incidences of the type of delivery and of the infantile and maternal mortality for each age group.

TABLE X. RESULTS ACCORDING TO AGE GROUPS

AGE	TOTAL CASES	INCIDENCE					AVERAGE DURATION LABOR (HOURS)
		TYPE OF DELIVERY		CESAREAN SECTION	MORTALITY		
		SPONT.	OPERATIVE		INFANT	MATERNAL	
35	244	50.0	50.0	8.6	9.0	0.0	20.57
36	180	41.7	58.3	10.5	5.5	0.6	21.22
37	149	44.3	55.7	11.4	7.3	0.7	20.76
38	87	39.0	60.9	16.1	12.6	1.1	21.24
39	66	43.9	56.1	24.2	1.5	1.5	18.80
40	48	45.8	54.2	16.7	8.3	2.1	17.87
41	25	40.0	60.0	20.0	8.0	0.0	20.25
42	21	28.5	71.5	38.1	4.7	4.7	18.84
43	6	33.3	66.7	50.0	0.0	0.0	19.66
44	2	50.0	50.0	0.0	0.0	0.0	11.16
45	1	100.0	0.0	0.0	0.0	0.0	26.20
46	1	100.0	0.0	0.0	100.0	0.0	10.05

Episiotomy was performed in 65.5 per cent of the vaginal deliveries and a third-degree tear of the perineum occurred in 0.5 per cent of the

cases. In the clinic as a whole the incidence of episiotomy is 55.0 per cent and of third-degree lacerations 0.9 per cent. In this clinic the loss of 600 c.c. or more of blood (excluding cesarean section) constitutes a post-partum hemorrhage. The incidence in this series was 6.0 per cent as compared to 2.3 per cent for the clinic as a whole. Most of the hemorrhages were due to uterine atony. Analgesia during labor was given in 60.7 per cent of the cases. The types used either alone or in combination were morphine, scopolamine, sodium pentobarbital, paraldehyde, and rectal ether. There was no instance where a fetal death could be attributed to the type of analgesia employed. Gas, oxygen, and ether was the anesthetic most frequently used; 78.6 per cent of the patients received this combination at delivery. Ethylene, cyclopropane, ether, avertin, gas-oxygen or local were used either alone or in combination in the remaining cases.

In the 830 elderly primiparas, the incidence of puerperal infection was 12.04 per cent and of puerperal morbidity 13.61 per cent as compared to 6.0 per cent and 7.9 per cent, respectively, for the clinic as a whole. By puerperal infection is meant a rise in temperature to 100.4° F. (38° C.) occurring once during each of two twenty-four-hour periods following delivery or remaining elevated longer than twenty-four hours, excluding the first twenty-four hours after delivery, unless the rise in temperature is definitely proved to be due to other causes such as mastitis, pyelitis or intercurrent infection. Morbidity includes all cases of puerperal infection and all those febrile from other causes. The following table shows the distribution of the types of morbidity.

TABLE XI. PUERPERAL MORBIDITY

CAUSE	CASES
Puerperal infection	100
Febrile, mastitis	4
Febrile, pneumonia	3
Febrile, urinary tract	5
Febrile, other	1
Total	113
Incidence, puerperal infection, 12.04 per cent	
Incidence, puerperal morbidity, 13.61 per cent	

The following table shows the complications of pregnancy that occurred either during the ante-partum or post-partum period.

TABLE XII. COMPLICATIONS OF PREGNANCY AND THE PUERPERIUM

COMPLICATION	NUMBER OF CASES	INCIDENCE
Ante-partum bleeding	13	1.6
Premature separation of placenta	3	0.3
Placenta previa	5	0.6
Urinary tract infection	19	2.3
Thrombophlebitis	8	0.9
Toxic psychosis	1	0.1
Postoperative ileus	5	0.6
Peritonitis	5	0.6
Prolapsed cord	2	0.2
Mastitis	4	0.4
Pneumonia	5	0.6

It is seen from this table that the incidence of ante-partum bleeding is 1.6 per cent; in the clinic as a whole it is 1.3 per cent. The incidences of premature separation of the placenta and placenta previa are 0.3 per cent and 0.6 per cent, respectively, as compared to 0.4 per cent and 0.5 per cent in the total clinic population.

There were six maternal deaths in the group of 830 elderly primiparas. The incidence of maternal mortality is, therefore, 0.72 per cent (7.2 per 1,000 pregnancies) as compared to 0.16 per cent (1.6 per 1,000 pregnancies) for the clinic as a whole. In five of these six cases, death occurred following cesarean section. Three of the deaths were due to infection. These occurred in two classical cesarean sections and in one low cervical section, the indications for the operations being acute yellow atrophy, contracted pelvis, and myoma uteri. None of these patients had had any antecedent labor. The ages of these three patients were 36, 38, and 42, respectively. The fourth death was due to hemorrhage following a low cervical section performed after 15½ hours of labor, the indication being cephalopelvic disproportion. The age of this patient was 40 years. The fifth death was due to cerebral embolus which occurred on the fifth postoperative day. This patient, aged 37, had a low cervical section after 21 hours and 56 minutes of labor without progress. The sixth patient, aged 39, died 55 minutes after a full-term mid-forceps delivery which was performed after 27 hours of labor because of fetal distress. Death in this case was due to circulatory collapse which was presumed to have been precipitated by a pituitrin reaction. The three patients in whom death was due to infection following cesarean section had no labor preceding the operation. One patient developed a generalized peritonitis with intestinal obstruction which necessitated an ileostomy. Death occurred on the twelfth postoperative day. The other two patients of this group died on the seventh and tenth postoperative days, respectively; one had, in addition, a femoral and pelvic thrombophlebitis. The deaths from peritonitis all occurred before the advent of sulfonamide therapy. In at least two of the six cases, death might have been obviated. In the case of the death from hemorrhage, the course undoubtedly would have been altered by more expeditious and intensive treatment of the accompanying shock. In the case of the cesarean section performed because of myoma uteri, more radical surgery would appear to have been indicated. Recent studies have shown that in the presence of large myomas of the uterus, the morbidity and mortality rates following cesarean section are diminished if hysterectomy is performed. The following table shows the incidence of mortality in the entire group and in the cesarean section group.

TABLE XIII. MATERNAL MORTALITY

	INCIDENCE	
	TOTAL GROUP	CESAREAN SECTION
Elderly primiparas	0.72	4.49
Total clinic	0.16	1.52

It has often been thought that the weight of the infant of the elderly primipara is greater than average. We have not found this to be true. The average weight of the full-term infants in this series was 3,380 grams, and the average weight for full-term infants in the clinic as a whole is 3,350 grams. The largest infant among the elderly primiparas weighed 5,200 grams and the smallest 1,190 grams. There were 8.2 per cent of the infants that weighed 4,000 grams or over as compared to 10.5 per cent for the clinic as a whole. The incidence of premature infants was 6.0 per cent as compared with 3.6 per cent for the clinic. This greater incidence of prematurity has been reported by others in the literature.<sup>8</sup> There were six sets of twins in the entire group. With regard to the sex of the infants, 51.3 per cent were males and 48.7 per cent females, a ratio of 106:100.6.

In this study of 830 cases (836 infants) there were 64 infantile deaths, an incidence of 7.65 per cent as compared to 3.71 per cent for the clinic as a whole. There were 43 autopsies (67.1 per cent) performed, but no definite cause of death could be found in 35 per cent. There were 45 deadborn infants, 3 stillborn, and 16 neonatal deaths. The following table shows the time of death in utero of the 45 deadborn infants.

TABLE XIV. TIME OF INTRAUTERINE DEATH

TIME	CASES	INCIDENCE
Before onset of labor	15	33.3
During first stage	20	44.5
During second stage	10	22.2
Total	45	100.0

It can be seen that in 66.6 per cent of these cases death occurred during labor. Since 22.2 per cent occurred during the second stage, it would follow that interference at an earlier time would have been justifiable. The causes of death in this group were three intracranial injuries, three intrauterine asphyxia of which the cause was not clear, one asphyxia due to loops of cord around the neck, and three unknown. The types of delivery in this group were: three midforceps (one with Dührssen's incisions), three low forceps, one high forceps with Dührssen's incisions, one failed forceps with craniotomy, and two breech extractions.

The following table shows the cause of death and type of delivery in the infantile mortality group.

TABLE XV. INFANTILE MORTALITY

CAUSE OF DEATH	NUMBER OF CASES			
	DEADBORN AND STILLBORN		NEONATAL DEATH	
	SPONTA-NEOUS	OPERATIVE	SPONTA-NEOUS	OPERATIVE
Intracranial hemorrhage	0	6	0	3
Congenital anomalies	2	1	2	1
Asphyxia	1	3	0	3
Pneumonia	1	0	0	2
Unknown	15	19	3	2
Total	19	29	5	11

Of the 785 live infants discharged from the hospital, 51 had some complications. There were 16 with congenital abnormalities, such as clubfoot, harelip, and cleft palate or imperforate anus. Eight infants had an infection—impetigo, diarrhea, or thrush. Four others had hemorrhagic disease. There were 23 with traumatic injuries; five of these had cerebral hemorrhage. The other injuries were fractured clavicle or humerus, cephalhematomas, and brachial palsy.

### Discussion

It is quite evident from the figures presented in this paper that the results obtained in the care and delivery of the elderly primipara can be improved. From the time the patient first presents herself for obstetrical care until after delivery, she must be carefully studied and closely followed. Detailed information must be obtained concerning the pelvis, and at term the size of the infant estimated as accurately as possible. The expected date of delivery must be ascertained, for it is seen that in patients who go more than two weeks past term, the labor is longer and the infant mortality higher. In patients who do go past the expected date, operative interference should be considered, especially if any complication is present. A normal individual who marries late in life and who is delivered of a full-term or premature infant at 35 years of age or over, may have no complications at the time of delivery. In patients giving a history of a long period of infertility, without the use of contraceptives, operative delivery should be carefully considered. In the older patient myoma uteri and toxemia are the two most frequent complications to be found. The incidences of operative procedures and of infantile and maternal mortality are much higher in this group of elderly primiparas, but as our knowledge of obstetrics progresses, we feel these can be readily improved. Conservative treatment is at all times the best policy to follow, but very often what seems to be a radical procedure, in the case of the elderly primipara becomes a conservative one.

### Summary and Conclusions

1. The incidence of elderly primiparas in this clinic was 2.68 per cent.
2. The incidence of toxemia of pregnancy in these patients was 13.98 per cent as compared to 7.29 per cent in the clinic as a whole.
3. Myoma uteri occurred in 5.9 per cent of the elderly primiparas as compared with 1.9 per cent in the total clinic.
4. Although the incidence of contracted pelvis in this series was 13.0 per cent in contrast to 9.2 per cent for the total clinic, the greatest difference appeared in the incidence of funnel pelvis. This type made up 45.3 per cent of the contracted group in the elderly primiparas and 28.2 per cent in the clinic.
5. When the elderly primipara goes two weeks or more past the expected date of delivery, the incidence of prolonged labor is 28.91 per

cent, of operative delivery 69.87 per cent and of infantile mortality 24.09 per cent, as compared with 17.59 per cent, 55.54 per cent and 7.64 per cent, respectively, for the entire group of elderly primiparas.

6. The average duration of labor for this group was 20.41 hours. The average duration of labor for primiparas in the clinic is 18.0 hours.

7. The incidence of operative deliveries was 55.54 per cent and of cesarean section 13.38 per cent, while in the clinic as a whole, these incidences are 24.3 per cent and 2.9 per cent, respectively.

8. The gross infantile mortality was 7.64 per cent as compared to 3.7 per cent for the clinic as a whole.

9. The maternal mortality was 7.2 per 1,000 pregnancies as compared to 1.6 per 1,000 pregnancies for the total clinic.

10. The mere fact that a patient is an elderly primipara is not in itself an indication for cesarean section. If, however, there is an added factor which under any circumstance would be an indication for cesarean section or would increase the fetal mortality rate, this operation is justifiable. For it is recognized that in selecting the type of delivery for this group of patients, the greater importance of the fetus does play a role. This is especially true when the patient gives a long history of relative sterility or of repeated spontaneous abortions.

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### Discussion

DR. GEORGE H. RYDER.—The statistics just given were compiled from ward patients. It might be of interest to compare these with statistics compiled entirely from private patients. In my first 1,400 consecutive deliveries of private patients, the incidence of elderly primiparas was about 1 in 24 (4.2 per cent). Comparison with the whole series of 1,400 women shows the following:

The incidence of toxemia of pregnancy was 3 times higher, as was that of eclampsia. The incidence of occiput posterior positions was 50 per cent higher, while that of spontaneous rotation was lower (one-fourth of all in contrast to over one-third).

The incidence of operative deliveries was much higher, over three-fourths in contrast to less than one-third. Cesarean sections constituted one-fourth in contrast to 3.7 per cent; and forceps deliveries over one-half in contrast to one-fourth. The incidence of high forceps was more than 3 times as great, that of medium forceps over twice as great, and that of low forceps more than 50 per cent greater.

The incidence of placenta previa was 3 times higher; that of prolapsed cord 5 times higher; and that of tamponade of the uterus in pelvic deliveries, 2½ times higher. Fibroids were found in about 1 out of every 5 elderly primiparas.

The average length of labor was considerably greater. The incidence of long labors (36 hours or more) was 3 times higher. The total fetal mortality was almost twice as high; that from dystocia 3 times as high, and that from other causes 50 per cent higher.

Among the 1,419 babies of the series, there were 8 hopeless defectives. Two of these, Mongolian idiots, were among the babies of the 59 elderly primiparas, an incidence 6 times higher.

The morbidity (temperatures of 100.6 F. for 48 hours) among the elderly primiparas was more than 3 times higher than among the women of the whole series, that from puerperal causes  $3\frac{1}{2}$  times higher, and that from nonpuerperal causes 3 times higher. The maternal mortality was more than 12 times higher, the two deaths occurring among the 59 elderly primiparas being half of all maternal deaths among the whole series of 1,400 women. Among these 1,400 women, only one young woman died, from gripe pneumonia in the epidemic of 1918. The other three deaths were in women at or near the age of forty, 1 from pulmonary embolus, 1 from pneumonia following toxemia of pregnancy, and 1 from a ruptured appendix with operation refused.

It seems clear that elderly primiparas, not only have harder times in labor, but that they are more susceptible to complications in pregnancy and the puerperium.

DR. EDWARD G. WATERS.—This presentation is of immediate clinical interest for we see a large number of elderly primiparas in contrast to years ago. The elderly primiparous patient is interested in her chances as compared to those of her sister fifteen years younger. From a purely obstetric standpoint, her outlook is little if any worse than that of a girl of twenty who happens to be pregnant, if one accepts the fact that she is fifteen years older and subject to all the hazards that the process of getting older entails.

I have been interested in this problem and in the last year Dr. Wager and I have been checking the elderly primiparas at the Christ Hospital. We have taken the same age standard of 35 years or more for classifying these women as elderly and we have some rather interesting data. We do not see nearly as many in our clinic, proportionately, of these elderly or old primipara as recorded here tonight. In our hospital there were only 312 in 25,860 deliveries.

It is hard to tell when a woman is old from the standpoint of having babies. We wished to have data by which we could compare the experiences of old and young women. A woman of 35 or more is certainly old to have her first baby. Between 15 and 25, patients are in the first ten-year period of their child bearing years. So if you compare the old group with the young group, you get a fairly good idea of the hazards to those women who get pregnant in the third period of their child bearing years. We took, year by year, the same number of young primiparas to compare with this group of 312 elderly primiparas from a group of over 25,000 cases from 1938 to 1941. In the elderly group, 116 were 35 years of age; 64 were 36 years old; 43 were 37 years old; 34 were 38 years of age; 28 were 39 years old; 11 were 40 years old; 7 were 41 years; 7 were 42 years; 1 was 43 years old; and 1 was 47 years.

To record duration of labor, we grouped these young and old primiparas into 4-hour periods, up to 24 hours, and then into 6-hour groups to 42 hours. The remainder varied from 42 to 60 hours and over, with the time of labor unrecorded in 53 cases. Although 312 cases represent a small group from which to draw conclusions, nevertheless we could find no really significant difference in the hours of labor between the elderly and the young primiparas.

As far as the weight of the babies is concerned, we took all the babies under 2,500 grams, those from 2,500 to 3,500, which would be approximately in the normal range of birth weight, those from 3,500 to 4,000, and those over 4,000 grams. In the group between 2,500 and 3,500 grams there were 172 elderly primiparas and of the young primiparas, 180. This represents no significant difference.



We considered toxic conditions of pregnancy, and found that the elderly primipara, had a toxemia incidence almost three times as great. Twenty-nine of the elderly primiparas had eclampsia, hypertension, pre-eclampsia and nephritic type of eclampsias, as compared to 10 in the young primiparas.

There were 15 cases of fibromyoma uteri in the elderly primiparas and none in the young primiparas, as would be expected. Heart disease occurred 10 times in the elderly primiparas as compared to twice in the young group. Abruptio placenta occurred about equally in both groups, 7 and 6 respectively. Placenta previa occurred 4 times in the older group and never in the younger group. Postpartum hemorrhage was approximately the same, there being 7 in the older group and 10 in the younger group.

In our women we found no essential difference between the two groups with respect to soft part dystocia. The operative experience of these women was certainly different and I think for good reason. Low forceps was employed about the same number of times for both groups. Midforceps are used about two and a half times more often in the elderly than in the young primiparas.

We had almost the same percentage of cesarean sections in our group as was shown here, 42 of the low, transperitoneal laparotomelotomy type, and 17 extraperitoneal sections, a total of 59 in the elderly primiparas as compared to 7 in the younger group. Of these 5 were low flap and 2 extraperitoneal.

The morbidity rate was about twice as great in the elderly primiparas as in the young primiparas.

There were 245 live babies in the elderly primiparas as compared to 292 in the young primiparas, but the premature nonviable infants in the elderly primiparas were much higher.

Our cesarean incidence is comparable to that reported here this evening. It is high but I think rightly so. There are other factors in elderly primiparas more important than their age. When these patients over 35 come to us pregnant for the first time, some of them married for many years, the baby assumes a social importance that is in no way comparable with the baby of a young healthy primipara. The loss of a first baby in a woman of 35 is a real tragedy for it may be her only child. The concurrent fact that she is more subject to the hazards of degenerative diseases of the last third of her childbearing life makes this pregnancy in this patient more likely to be terminated by cesarean section.

Dr. Johnson's figures certainly show the hazard of classical section. I think those three deaths from peritonitis and sepsis, and 1 following the low flap operation might well have been eliminated by different choice of operation. In our series there were 42 low flap and 17 extraperitoneal sections done on elderly primiparas with no deaths. In the young primiparas we did 2 extraperitoneals out of 7 sections, and those were infected and bad risks.

In the entire group of 312 elderly primiparas we had 2 deaths, 1 from cardiac disease before leaving the hospital, and 1 from pulmonary embolism. There were no deaths in the section group. I think that one might stress the importance of not doing any classical sections on any women, and secondly on any potentially or actually infected woman, choose an extraperitoneal rather than a low flap operation. In more than 400 extraperitoneal sections on potentially and frankly infected women, we have had only 4 deaths in the last 10 years.

DR. WILLIAM S. SMITH.—The elderly primipara is a hazard during pregnancy and labor. I believe such a patient should be very carefully considered as to whether she is physically sound and, secondly, as to the probabilities of her being able to withstand a pregnancy and labor.

All elderly primiparas require more rest and more careful watching during pregnancy and labor than is required by younger patients. The obstetrician must be constantly on the watch for early symptoms which may indicate that the pregnancy load is too heavy.

I prefer not to induce labors in these patients before term because such induced labors are often long and difficult. If, after a six- or seven-hour test of labor, a long and difficult labor is probable, a cesarean section should be done at once while the patient is in good condition to withstand the operation.

DR. MEYER ROSENTOHN.—Dr. Johnson's statement in his last paragraph gives his basic conclusion: no cesareans for elderly primigravidas as such, but the presence of any complications or any associated factors which would endanger the life of the baby, warrant this operation. I agree with this. Dr. Smith puts it properly in allowing these patients a test of labor of four to six hours, although I do not subscribe to such a definite period. I should like to refer to two patients we had at the Bronx Hospital who come in this category.

1. A patient, 42 years of age, due December 10, last was admitted November 2, with a history of eight miscarriages, only one of which occurred as late as the seventh month. She had a basal metabolism of plus 40 and exophthalmos. The baby was a fair size ( $7\frac{1}{2}$  pounds). She had a polyhydramnios and with the fear of a monstrosity, no cesarean was done. The membranes ruptured spontaneously the next day and after some forty hours, she delivered a healthy, normal baby spontaneously.

2. This patient was the first to introduce me to a term which many of you have undoubtedly heard before, "The change of life baby." She was 44 years of age, married twenty-seven years, and had had an ectopic eighteen years before. She was due August 25, and was found to have a baby which was not large. The matter of cesarean section was explained to her and she was willing to take some of the responsibility. After some forty hours, a midforceps was done and a living normal baby weighing 6 pounds, 10 ounces was obtained. In both these cases the operations, if done, would not have been criticised, and yet both patients were delivered of normal babies per vaginam with no difficulty.

DR. JOHNSON (closing).—There are few problems which offer a greater challenge to the judgment of the obstetrician than that of managing the elderly primipara. The increased value placed on a live infant might cause one to be radical, but we must bear in mind the fact that with radical treatment the maternal organism is undoubtedly subjected to an increased risk. We feel that if more attention is paid to some of the factors outlined, the results in this small, but important, group of patients will be improved.

# THE POSSIBLE SIGNIFICANCE OF VAGINAL SMEARS IN THE DIAGNOSIS OF CERTAIN DISTURBANCES OF PREGNANCY\*

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AS EARLY as 1917, Stoekard and Papanicolaou<sup>1</sup> described the technique of the vaginal smear in studying the estrous cycle of the guinea pig. More recently (1933) the latter<sup>2</sup> studied the cyclical changes in the human vagina with changes in the endometrium. His monograph in the *American Journal of Anatomy*, May, 1933, is monumental, and includes the changes in the vaginal spread or smear not only during the different phases of the menstrual cycle, but also during pregnancy and the puerperium. The earlier work of Stieve in connection with the changes during pregnancy (1925) is quoted by Papanicolaou in his classic.

In relation to these studies in the histology of the human vagina, many interesting and fascinating developments in the endocrinology of the female reproductive system have occurred. The discovery of the typical estrous reaction of the vagina of rodents by Papanicolaou and Stoekard, Long and Evans, and Allen and Doisy made possible the qualitative and quantitative determination of estrogenic hormone. This was followed by the demonstration by Aschheim and Zondek of female sex hormone in the Graafian follicle, placenta, and later in the urine of pregnant women. Subsequent to this came their discovery of large amounts of gonadotropic hormone in urine of pregnant women, with the well-known pregnancy test. Out of the classical experiments of these workers came the essential facts that the follicle or estrogenic hormone stimulates the vagina, and the gonadotropic hormone, the ovary (corpora lutea).

While the Aschheim-Zondek test and the more recent modification of Friedman are based on gonadotropic reaction, the vagina of the rodent has not been given up as a criterion for pregnancy reaction. Zondek has developed a pregnancy test for mares based on the estrous reaction of the vagina of the rat. Mazer<sup>3</sup> employs the estrin test alone or in conjunction with the Friedman test for the diagnosis of early pregnancy. He uses the castrated adult female mouse, and his criterion for a positive test is finding a preponderance of non-mucinated epithelial cells and the absence of leucocytes and mucus.

Interest in the pregnant woman from the endocrine point of view has not ceased with the diagnosis of pregnancy.

\*Read at a meeting of the Baltimore Obstetrical and Gynecological Society. November 12, 1943.

In 1933, Spielman, Goldberger, and Frank,<sup>4</sup> realizing that neither the Aschheim-Zondek nor Friedman test can be used to determine the question of the life or death of the fetus (because of the presence of active chorionic tissue after fetal death), utilized the blood estrin levels as an indicator of whether the fetus is alive or dead. These investigators report that beginning at the middle of the second month, the estrin titer constantly increases (the source of the hormone being the placenta). They found a reduction in the blood estrogenic factor within 24 hours after fetal death. More recently, Goldberger and Frank<sup>5</sup> found that the seventeenth week of pregnancy is the point at which typical pregnancy levels of estrogen begin, and that from then on there is a progressive increase to the end of pregnancy. In their earlier article, they claim that the Frank-Goldberger estrin determination is more sensitive than the pregnancy tests based on gonadotropic hormone.

The quantitative estimation of pregnancy hormones in the blood and urine of pregnant women was utilized by Smith and Smith<sup>6</sup> in 1935 in studying toxemias of late pregnancy. They found excessive amounts of prolactin and subnormal levels of estrin to be typical of the late toxemias. Similarly, Anselmino in 1936,<sup>7</sup> performed experiments tending to confirm observations previously made by Heim that in hyperemesis there is an increased excretion of prolactin. It has also been shown that excessive amounts of pituitary gonadotropin depress the production of estrogen, and vice versa.

In all these far-reaching advances in endocrine research, the reaction of the patient's vaginal mucosa, that is, the vaginal smear of the patient herself, was not utilized until Papanicolaou and Shorr in 1935 and 1936<sup>8</sup> demonstrated the changes in the smear of a menopausal patient treated with estrogenic hormone. The menopause, with its sudden and dramatic alteration in reproductive physiology and its attending quantitative hormonal changes, furnishes an ideal laboratory for the study of the vaginal smear. Therefore, the menopause has been the subject of widespread study in this field of research. And yet, the condition in which modern endocrinology had its birth, namely pregnancy, remains unexplored, insofar as concerns the study of the vaginal smear beyond the strictly anatomic phase, as performed by Papanicolaou and Stieve. With their work as a basis, and making use of the improvements in staining technique of Shorr,<sup>9</sup> Geist and Salmon,<sup>10</sup> and others, the vaginal mucosa of the pregnant woman deserves the most painstaking study for the detection of variations from the normal, leading possibly to important clinical interpretations. Beginning with the very diagnosis of pregnancy itself, why could not technique be so refined that the simple taking of a smear on the patient would suffice to settle the question? Bearing in mind the quantitative changes in blood estrin levels found by Frank and Goldberger, it is not illogical to suppose that the life or death of the fetus could be determined by the vaginal smear. If the toxemias have a hormonal basis (as many now believe), may we not have a means through the vaginal smear of detecting a toxemia before the usual clinical signs appear, and also of differentiating one type of toxemia from the other? Perhaps, some day soon the vaginal smear may reveal what an eye ground now portends. The question of abortion from blighted ovum or other cause (a subject in which Rutherford<sup>11</sup> has become so interested as to perform biopsy on the decidua) might be answered by the vaginal smear. Even if it were not possible to attain the ultimate, such as the afore-mentioned, it would be a great step for-

ward to add to our clinical tests a simple procedure that would correlate certain disturbances of pregnancy with the histology of the vagina.

Papanicolaou, it will be remembered, made no effort to identify a histologic picture with any disturbance of pregnancy. His observations were made apparently from normal pregnancies of known periods of gestation, an anatomic study. Very few individuals to date have endeavored to correlate the vaginal smear of pregnancy with a definite clinical entity. Fletcher<sup>12</sup> (1940) studied the histomorphology of the vagina with special reference to changes observed in cases of incomplete abortion. Using the staining methods of Papanicolaou with modifications, he found certain details in his smears that he suggested might be characteristic of incomplete abortion. Greenhill mentions, in the 1942 Year Book of Obstetrics and Gynecology, a study by M. R. Cohen and B. B. Rubenstein,<sup>13</sup> reported before the Chicago Gynecological Society in November, 1942, in which vaginal smears were taken and studied in 500 consecutive patients, including pregnant and nonpregnant women. These workers state that the smear in pregnancy is sufficiently typical as to distinguish pregnancy from nonpregnant states. They succeeded in diagnosing pregnancy in 84 per cent of 200 "unknowns." M. J. Bennett and P. B. Russell, Jr.<sup>14</sup> (1941) included in the examination of 15,000 slides some vaginal smears of female fetuses as early as 18 weeks' gestation and corresponding smears in the mothers. They show that the fetus exhibits a follicular stimulation until birth, which gradually decreases until the baby is 94 days old, when it disappears entirely. At 7 months' gestation, the maternal smear shows a predominant follicular influence. The same authors and L. C. Ramsey<sup>15</sup> (1941) studied the vaginal smears in 50 women throughout pregnancy, together with blood estrogen studies, basal metabolic rates, etc. They found close agreement between pregnancy and the normal menstrual cycle.

Grossly, changes in the human vagina as a result of pregnancy have been observed to an extent more exaggerated than the usual textbook description of mere lengthening and increased vascularity. The most striking illustration of anatomic adaptation of the vagina to pregnancy occurred in a patient of the author thirteen years ago.

A recently married young woman consulted me quite disturbed because a gynecologist had just told her she could never have a child except by cesarean section, as her vagina was poorly developed. On examination, I found the vagina stenosed in its middle third, an hour-glass type of stenosis, so that one finger could not get all the way through to the posterior portion. Any attempt to stretch the stenosis was attended by a mild degree of shock. Despite the warning of the gynecologist, I advised the patient to get pregnant, and see "what Nature would do." She promptly conceived, and I examined the vagina at regular intervals throughout the pregnancy. In the early months, very little change could be detected, but at the end of the second trimester definite softening and dilatation of the stenotic portion was apparent, and at about 7 months' gestation, to my great satisfaction and that of the patient, the stenosis had spontaneously corrected itself about 75 per cent, and before labor, about 90 per cent. The result was that the patient delivered per vaginam with the aid of low forceps. The stenosis was permanently cured, and a second pregnancy was uncomplicated by that condition.

This incident impressed me more and more as female endocrinology and reproductive physiology were revealed, for here was a perfect

example of the maturing effect of hormonal stimulation by the high estrogen level of pregnancy on the development of the vagina grossly. Had this case occurred more recently, it would have been possible by the vaginal smear technique to demonstrate the hormone effect histologically.

Histologically, the vaginal mucosa in the normal adult female consists of stratified squamous epithelium of considerable thickness. There is (1) a basement layer of cells known as the basement membrane, next to which is (2) an inner basal zone of small round cells with fairly large nuclei; then (3) a thick layer, known as the functional layer, with larger cells and more varied in shape; and finally (4) a superficial cornified layer, consisting of large, flat, polyhedral squamous cells with small pyknotic nuclei. In conditions of estrin deficiency, such as the menopause, the mucosa becomes thin due to the disappearance of the functional and cornified layers. The smear shows the deep cells known as "atrophy cells," which are small and round with large nuclei, and the presence of large numbers of leucocytes. On the other hand, in conditions of high amounts of estrin, of which pregnancy would be the best example, maximum proliferation of the epithelium of the vagina occurs. Hence, we find in the smear very large numbers of cornified cells of the superficial layer.

The classical studies of the vagina during pregnancy quoted by Papanicolaou, as mentioned before, are those of Stieve (1925).<sup>2</sup> He found in early pregnancy active proliferation, the epithelium increased enormously in thickness, reaching a maximum of 450 to 500 microns toward the end of pregnancy against an average thickness of 115 to 300 microns for the nonpregnant condition. There is an increase in the number of cells as well as their size, and in the size of the nuclei. Large cells, either isolated or in groups, appear more particularly in early pregnancy. The cornification is, as a rule, not very pronounced, but in many cases one may find nucleated cornified cells. In later pregnancy, Stieve saw cells of larger size with large nuclei and not as numerous as in early pregnancy. Nucleated cornified cells become more and more rare, but the anucleated eosinophilic cells gain in prominence in late pregnancy, and often occur in large heavy groups. Crowded cells and a high cellular disintegration with liberation of nuclei are often characteristic, according to Stieve.

### Material and Results

In order to attempt to correlate the classic histologic studies of Papanicolaou and Stieve on the vagina of pregnancy with the endocrinologic advances of recent years mentioned earlier in this article, the author decided to study a series of vaginal smears in pregnant women. Beginning in January, 1941, each prenatal patient in the obstetrical clinic of the Sinai Hospital had a smear taken by the dis-

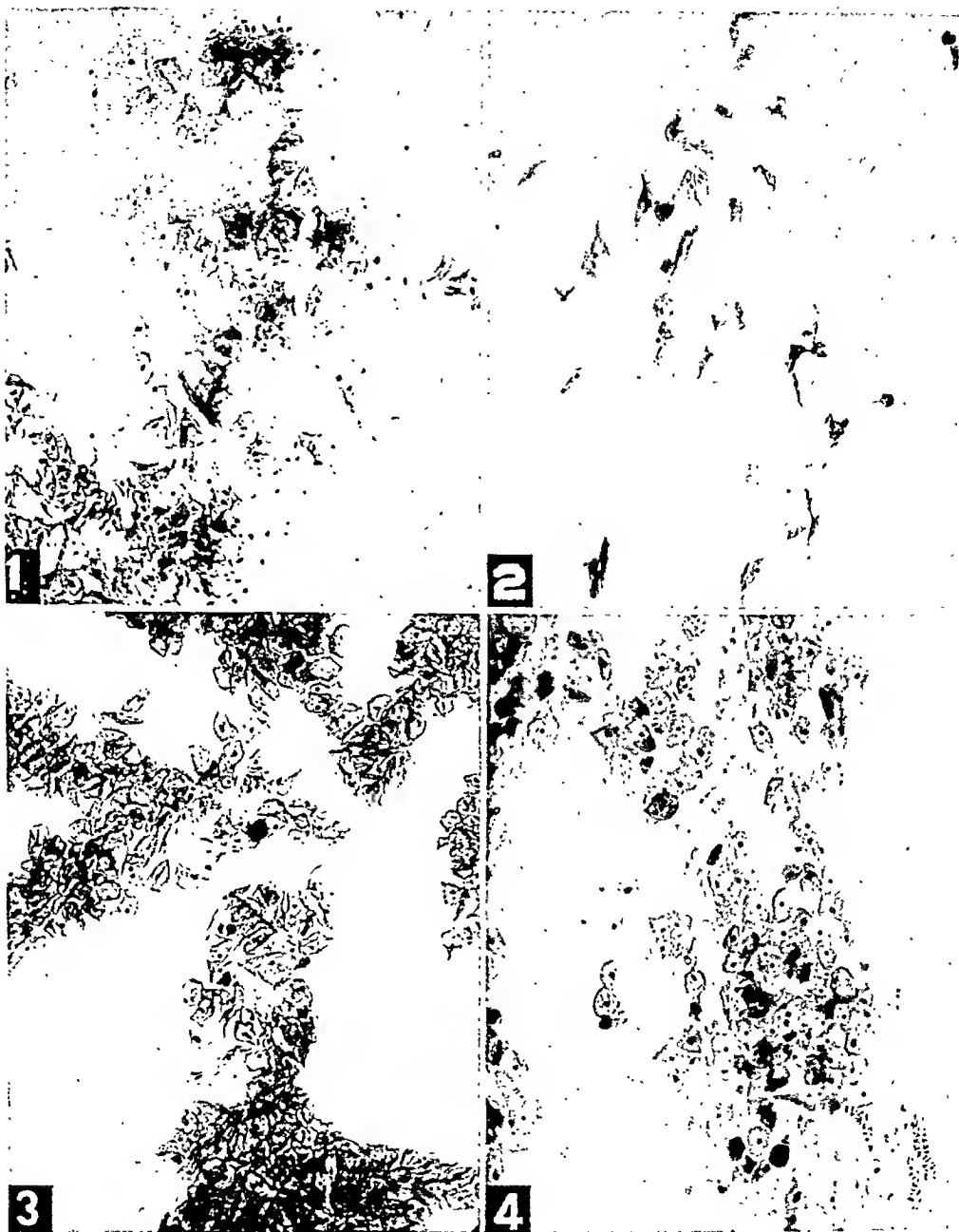


Fig. 1.—Case of normal pregnancy of 3½ months' gestation. Smear typical. Crowding of cells; cells moderately uniform; predominantly large cornified cells with small nuclei. No pus; no "deep" cells.

Fig. 2.—Case of missed abortion. Smear taken at 2 months' gestation. Diagnosis of missed abortion several weeks later. Smear shows no evidence of fresh cornification. Cells elongated and varied in size and shape. No large uniformly shaped cells.

Fig. 3.—Case of normal pregnancy. Ten weeks' gestation. Smear shows cells intensely in size and shape of cells striking; cells invariably large pus, mucus, bacteria, etc. strikingly devoid of other elements, such as

Fig. 4.—Case of early hypertensive toxemia (no vomiting) 4 months' gestation. Smear—Cells are smaller than in Fig. 3, but larger than in Fig. 1. There is not the same degree of uniformity as in Fig. 3.

pensary staff. Instead of the aspiration-pipette method, the technique used was rolling a cotton swab on the lateral vaginal wall. The smears were fixed immediately in alcohol-ether. The stain used was hematoxylin-eosin. About 350 smears were taken, every stage of pregnancy being represented. All smears were examined by the author.

Before going into a description of the smears selected for this paper, it is well to bear in mind that before any judgment can be passed on the value of smears, one must be thoroughly familiar with the normal varia-

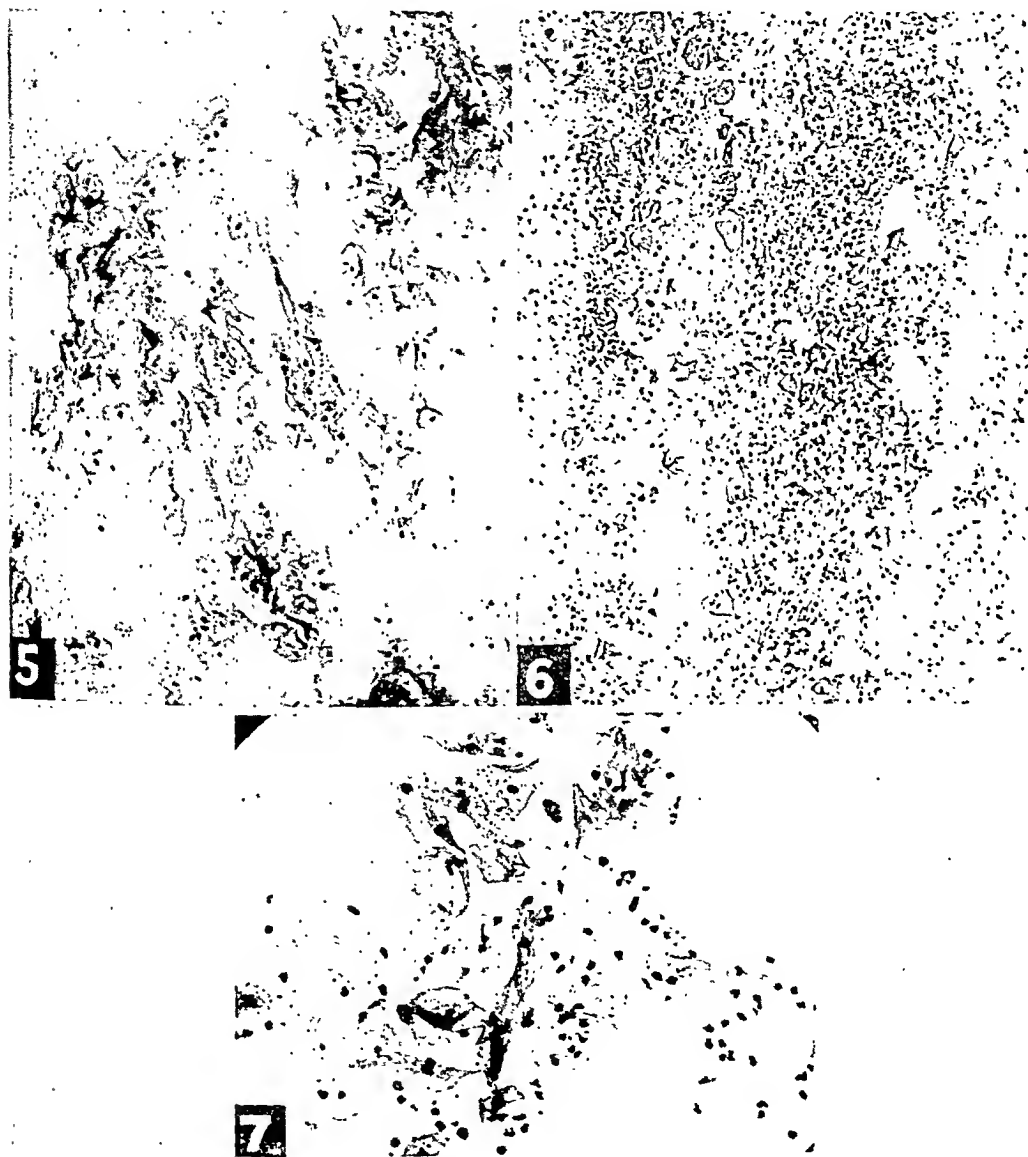


Fig. 5.—Case of normal pregnancy of 10 weeks' gestation at time of smear. Subsequently, patient had symptoms of threatened abortion lasting several weeks. Finally aborted at 5 months. Smear typical of normal pregnancy. (Compare with Fig. 1.)

Fig. 6.—Case of pre-eclamptic toxemia; stillbirth at 8½ months. Smear (taken at 6 months) shows large amount of pus. Many of the vaginal cells are of the deep or basal zone (small round cells with large nuclei).

Fig. 7.—(High power). Case of spontaneous abortion at 3 months. Smear (taken shortly before symptoms of abortion began) shows presence of pus cells. (No red blood cells.)



tions in cellular elements of the vagina. Papanicolaou himself states that no one but an expert in the cytology of the vagina can properly judge or interpret the vaginal smear. It goes without saying that, as a clinician the author cannot qualify in this respect. Accompanying each microphotograph, brief clinical facts are mentioned, so that the disorder of pregnancy can be correlated to the histologic appearance of the smear.

The author has not been able to demonstrate some of Stieve's findings, especially the difference between the smear of early and that of late pregnancy. To the average clinician with limited experience in histopathology, the chief characteristics of the pregnancy smear are the increased size and number of the cells, the presence of large numbers of eosinophilic cornified cells, and the absence of deep cells.

The degree of cornification in a large percentage of smears is so pronounced that it seems possible pregnancy might be diagnosed in this way, excluding nonpregnant states treated with large doses of estrogens. There is one condition which should be readily differentiated from pregnancy by the vaginal smear, namely, the menopause. This can be of great clinical value because of the numerous occasions on which the obstetrician or gynecologist is confronted with the problem of diagnosing a sudden amenorrhea in a 40- to 45-year-old patient.

The highest degree of cornification was seen in a case of hyperemesis. Not quite so marked, but definitely increased amount of cornification was also noted in a case of hypertensive toxemia (early). In a case of pre-eclamptic toxemia, smaller cells with larger nuclei, resembling cells of the basal zone, were seen, suggestive of estrin deficiency. This would go hand in hand with the findings of Smith and Smith<sup>6</sup> in their blood estrin determinations in the late toxemias. Comparison with the smear of the case of hyperemesis lends interesting speculation as to the relationship of the early and late toxemias. Those who have consistently opposed the neurotic theory of vomiting of pregnancy might find support for an organic etiology in the smears of a series of hyperemesis cases. Investigators on the trail of the toxemias by means of blood estrin levels might study the vaginal smears as a further index of hormonal disturbance in pregnancy.

In a case of missed abortion, fresh cornification was not present; cells were sparse, and appeared shrivelled. While there was no evidence of estrin deficiency, the usual picture typical of the response to pregnancy was not observed. If the vaginal smear could detect death of the fetus before clinical signs of abortion began, it would prove to be a much simpler method than the Frank-Goldberger blood-estrin test.<sup>4</sup> In a smear taken shortly before a patient had signs of a spontaneous abortion, pus cells were found. On the other hand, in a case where abortion was threatening for some weeks, the smear taken two months before

abortion showed no pus. The interpretation might be made that in the first case a blighted ovum with an abnormal hormonal response caused abortion, whereas, in the latter case, mechanical or local conditions in the uterus itself were responsible. In these two cases and in the case of missed abortion, therefore, we see three different clinical pictures and, correspondingly, three different types of smear. The ability to interpret correctly a vaginal smear in a patient before any bleeding or other symptoms of abortion occur may indeed be of great practical value in cases of habitual abortion where the cause is obscure, and where the physician seeks earnestly to employ rational therapy instead of that of the gunshot variety. For obvious reasons, smears taken after vaginal bleeding has begun are valueless.

A large amount of pus was found two months before a patient delivered a stillborn infant; this case, however, was complicated by toxemia.

In the author's opinion, pus is not a normal component of the vaginal smear of normal pregnancy, if the technique of the cotton swab rolled on the lateral vaginal wall is used. With the pipette method, the vaginal pool is aspirated, containing not only vaginal cells, but secretions of the cervix, such as pus and mucus, as well as microscopic blood from erosions and even from the interior of the uterus itself. Fletcher used the applicator, lateral wall method, but he took smears on women who had already aborted, and therefore he had to contend with blood elements and debris that came in contact with the lateral vaginal wall. It seems logical to state that in order to obtain a vaginal smear approaching the histologic detail of a true biopsy of the vagina, one must eliminate cervical and uterine secretions, and this can be accomplished only by the method described in detail by Fletcher<sup>12</sup> and used by the author.

### Summary

Approximately 350 vaginal smears taken on an equal number of patients during all stages of pregnancy were studied, and several smears of cases of different types of toxemias and different clinical varieties of abortion and fetal death are presented, and an effort is made to interpret them based on established hormonal variations in pregnancy, with especial reference to estrin levels. Making use of our constant gain in knowledge of the chemical properties and biological changes in the cells of the human vagina, yet realizing that a high degree of skill in the interpretation of the stained smear is required before widespread clinical application can be attained, it is suggested that histomorphologic patterns can be discovered in certain obstetrical conditions sufficiently clear to warrant the use of the smear as a definite aid in diagnosing and prognosticating disturbances of pregnancy. It is the purpose of this study and the hope of the author to stimulate interest in the use of the vaginal smear in obstetric practice.

Acknowledgment is made to Dr. M. W. Aaronson, retired head of the Department of Obstetrics of the Sinai Hospital for the support and encouragement of this study. Also to Dr. Tobias Weinberg, Director of Laboratories of Sinai Hospital, for his invaluable advice and generous assistance and cooperation, and to Mrs. Annette Nusinow, Miss Jessie Knight, and Mr. William Rickert for their technical assistance, without which this study could not have been completed.

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1716 EUTAW PLACE

## A SUGGESTED PROPOSAL FOR THE CLASSIFICATION OF TOXEMIAS OF PREGNANCY\*†

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THE American Committee on Maternal Welfare in 1939 elaborated a classification of toxemias of pregnancy as follows:

Group. A..Disease not peculiar to pregnancy:

1. Hypertensive or Arterial Vascular Disease

a. Benign {mild  
              severe, cardiorenal

b. Malignant

2. Renal Disease

a. Glomerulonephritis {acute  
                              chronic (mild or severe)

b. Pyelonephritis {acute  
                      chronic

c. Other forms of severe renal disease: Nephrosis, polycystic kidneys, and other congenital anomalies of the kidneys

Group B. Disease dependent on, or peculiar to, pregnancy:

1. Mild pre-eclampsia

2. Severe pre-eclampsia (preconvulsive)

3. Eclampsia

Group C. Vomiting of pregnancy

Group D. Unclassified toxemias

a. Those patients in whom a definite diagnosis cannot be made to allow them to fall into Group A or B (i.e., glomerulonephritis suspects).

b. Many will fall into the above-known groups post partum, but insufficient data before or in the early months of pregnancy make it imperative to exclude them from statistical data except when autopsy findings ultimately allow them to be put in either Group A or B.

The best that can be said for this grouping is that it represents an earnest effort toward uniformity in classifying these various conditions for study and thence for treatment. Its outstanding feature seems to be an attempt to divide such women into two groups, the first having recognized pathologic conditions predisposing to the crisis called the "toxemia of pregnancy," and the second embracing women apparently healthy in whom the "toxemia" was precipitated by the pregnancy. I believe that this is indeed weak and faulty, necessarily so because our knowledge of the precipitating causes of these acute conditions is so incomplete.

However, quite apart from such mild and hopeful criticism as this is another, and to me, extraordinary situation in this connection. This

\*From the revision now being prepared for the Third Edition "Management of Obstetric Difficulties" (Titus), The C. V. Mosby Co., St. Louis, under the John C. Oliver Memorial Research Foundation, St. Margaret Memorial Hospital, Pittsburgh.

†Read at a meeting of the Pittsburgh Obstetrical and Gynecological Society, February 7, 1944.

is that one member of the Committee (Foster Kellogg writing with Duncan Reid a few months after adoption of the Committee's report) undertakes to edit this grouping by deleting vomiting of pregnancy, or hyperemesis gravidarum, having "taken the stand that hyperemesis gravidarum (as well as acute yellow atrophy, previously omitted) is not related to the late toxemias of pregnancy." (See also Smith<sup>1</sup> of the same Boston group.) Apparently these two conditions were dropped because they usually occur early rather than late in pregnancy, even though others that were included, especially under Group A, may become manifest at any time, late or early. This seems to have made this classification more confusing rather than to have clarified it.

It seems even more logical to continue to include nausea and vomiting of early pregnancy as a recognized toxemia of pregnancy, than it does to add chronic pyelonephritis. Yet it is proposed to delete nausea and vomiting but to add pyelonephritis even though the latter is, actually, only an illness possibly predisposing to some of these other disturbances termed toxemias. It would be difficult to convince any woman seriously ill with hyperemesis gravidarum, or her family physician, that this is not a toxemic illness of pregnancy.

Those obstetricians who so universally favor the intravenous administration of dextrose solution in eclampsia may be interested to know that my<sup>2</sup> original suggestion of this for this purpose was directly an outgrowth of our observations on its beneficial effects in severe grades of hyperemesis. The arguments, now so familiar, were so logical and reasonable then in the days when hyperemesis was a toxemia and women still died of it, that they need not be recounted. The general adoption of this therapy and its benefits for both hyperemesis and eclampsia have served to do nothing else than strengthen my belief in the etiologic and clinical relationship of all of these toxic manifestations of early and of late pregnancy.

Criticism such as this would be unwarranted if not supported by a trial and its results. Williams and Weiss<sup>3</sup> attempted to tabulate 318 cases of toxemia of pregnancy under this classification, and have the following to say: "The application of this classification to material such as we have studied was not entirely satisfactory." They add, to soften the comment, "this was due in large part to the limitations of some of the material."

Criticism such as I have made would be mere faultfinding if nothing about it were constructive. Williams and Weiss offered suggestions for changes to amplify and strengthen the original classification, and I venture to suggest an entirely new classification which I believe answers most if not all of the objections raised about this other. As a matter of fact, no one knows the limitations of this first classification better than the authors themselves, as they freely announce (Mussey and

Hunt).<sup>4</sup> Until our knowledge of the etiology of toxemia is more advanced than it is now, any classification will be incomplete.

The one offered here is, quite frankly, the result of proposals and purposes expressed by the keen minds of that Committee, but it retains the more solid of the older views as to what may be considered by us as toxemias, why they develop, and also this viewpoint of their possible or even probable relationship to each other.

### Proposed Classification

- Group A. Toxemia types most common early in pregnancy (Nausea and vomiting)
  - 1. With demonstrable pre-existing, predisposing causes (including dietetic, or endocrine, or cardiovascular disturbances, alone or in combinations)
  - 2. Without demonstrable pre-existing, predisposing causes
- Group B. Toxemia types occurring without predilection to any time during pregnancy (Acute yellow atrophy of the liver, acute nephritis or other renal disease, acute hypertensive cardiovascular disease, and certain unclassified types)
  - 1. With demonstrable pre-existing, predisposing causes (including dietetic, or endocrine disturbances, or general physical defects), alone or in combination
  - 2. Without demonstrable pre-existing, predisposing causes
- Group C. Toxemia types most common late in pregnancy (Pre-eclampsia, and eclampsia)
  - 1. With demonstrable pre-existing, predisposing causes (including dietetic, or endocrine disturbances, or general physical defects, alone or in combinations)
  - 2. Without demonstrable pre-existing, predisposing causes

Unlike the other classification, this one makes pregnancy the common denominator, emphasizes the peculiar groups of symptoms which we have always been accustomed to think of as types of toxemia of pregnancy, and also relegates various predisposing causes for these back to a minor role rather than including any of them as a "toxemia."

It allows for inclusion of most of the current theories as to possible causation, and I cannot find any case in our series that could not be classified fairly satisfactorily under one or another of these tabulations. There may occasionally be some trifling overlapping in classification of a given case, but this is usually readily reconciled.

It allows for the view held by many that each type of toxemia of pregnancy is a separate entity unrelated to the others. It provides equally well for the opposite view, in which I believe so strongly, that there is a basic underlying relationship between all of these types, their outstanding symptoms varying only because of the influence of various modifying factors.

### Summary

1. The classification of toxemias of pregnancy proposed by the American Committee on Maternal Welfare has been found unwieldy and unworkable.

2. Its proposal suggests, however, that further attempts be made to devise a suitable classification in order that toxemias of pregnancy may be tabulated in an orderly fashion to permit study of their various general types.

3. A simpler and more inclusive classification is offered for consideration and use in this respect, if found acceptable.

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1015 HIGHLAND BUILDING

# INTRAVENOUS ADMINISTRATION OF VINBARBITAL SODIUM\* FOR INDUCTION OF OBSTETRIC AMNESIA

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THE selection of suitable agents for the production of amnesia and analgesia is doubly important in obstetrics as compared with any other field of medicine. The obstetrician must have continuous concern for at least two patients and any method he employs must produce a specific effect upon one and not upon the other and should not alter the vital processes of either the mother or child. The desirability, and indeed the necessity for inducing amnesia and analgesia during parturition is now universally recognized. Numerous agents and methods have been advanced which are purported to produce the desired effect and to avoid undesirable and dangerous side reactions. The obstetrician must remind himself continuously of certain fundamental requisites demanded of any drug or method employed to induce successful amnesia. These requirements are as follows:

1. Amnesia for pain. Somnolence and amnesia during the intervals are not difficult to induce but severe psychic trauma may be sustained unless complete or nearly complete recollection of pain is obviated. This is particularly pertinent today when most of the laity has been conditioned through popular channels of communication to fully expect "painless childbirth."
2. Maternal respiration and circulation should not be altered or depressed.
3. Labor should not be prolonged.
4. There should be no residual fetal or maternal toxicity (i.e., asphyxia and "hangover" respectively).

Prior to August, 1941, the results obtained by oral administration of vinbarbital sodium were most encouraging. In many instances, however, it was considered desirable and advantageous to employ an agent which would produce amnesia in a much shorter time than that required for any oral preparation. Because of our previous experience and the failure to observe any significant side reactions or alteration of blood pressure and respiration when vinbarbital sodium was given orally, it was suggested that this drug be prepared in a manner suitable for intravenous administration.

A preparation of vinbarbital sodium which could be given intravenously was provided during the summer of 1941, and from September of that year to May, 1943, obstetric amnesia was induced in 1,500 consecutive patients with this agent. The results observed in the last series,

\*Vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate, and is distributed under the name of "Delvinal" Sodium. The material used in this study was provided through the courtesy of Sharp & Dohme, Philadelphia, Pa.



consisting of 296 patients, have been subjected to a critical analysis and are contained in this presentation. The remainder of the consecutive series of 1,500 patients was similar in all respects to the one herein presented and was omitted only because of lack of time and personnel required for the detailed presentation of such a large survey.

The pharmacologic and clinical attributes of this drug, when administered orally, have been favorably reported upon by competent investigators.<sup>1-6</sup> The intravenous preparation is a solution of 1 gr. of vinbarbital sodium per c.c. in propylene glycol and distilled water. A standardized method for induction and maintenance of obstetric amnesia was established for the purposes of this study and administered to all patients during the course of the present investigation as follows:

### Method

When uterine contractions were noted at regular intervals of seven minutes or less, 3 to 5 gr. of vinbarbital sodium were administered intravenously over a period of approximately one minute. Immediately following the intravenous administration of vinbarbital sodium  $\frac{1}{130}$  gr. of hyoscine hydrobromide was injected intramuscularly. If delivery had not occurred within forty-five minutes,  $\frac{1}{260}$  gr. of hyoscine hydrobromide was administered intramuscularly and this dose was repeated in another forty-five minutes. Thereafter,  $\frac{1}{260}$  gr. of hyoscine hydrobromide was administered intramuscularly at ninety-minute-intervals as necessary to maintain amnesia. All patients were delivered under gas-ether anesthesia with the aid of prophylactic forceps, or by simple extraction if the breech presented.

Within twenty-four hours post partum, each patient was questioned closely concerning her subjective reaction to the method employed for production of amnesia and analgesia. The replies from 1,500 patients to whom the above outlined method was administered were as follows:

1. Complete amnesia, 90 per cent
2. Partial amnesia, 8 per cent  
(recollection of isolated events)
3. No amnesia, 2 per cent

### Results

The objective findings were equally encouraging. No noticeable change occurred in maternal blood pressure, or in the cardiac or respiratory rates. This is in marked contrast to our previous experience with another barbiturate administered intravenously which produced a high percentage of maternal respiratory depression. The fetal heart sounds were unaffected. There was no slowing or interruption in the progress of labor. In a number of instances induction of amnesia, with vinbarbital sodium was started early in labor with deliberate intention to determine whether or not administration of this drug would interrupt or slow the progress of labor. No tendency for any delaying

activity was ever observed. The incidence of post-partum hemorrhage was 2 per cent which was practically identical with that currently observed in patients on other obstetric services and regardless of the fact that sedation had or had not been employed. There was no mental depression (disorientation or "hangover") after delivery with the exception of one patient whose past history revealed unusual susceptibility to barbiturates. It was necessary in approximately 30 per cent of patients to resort to some mild application of restraint. This was soon discovered to be a hyoscine effect and not produced by vinbarbital sodium, since it occurred when hyoscine was administered alone. A study is now under way to reduce or eliminate the restlessness caused by hyoscine. There were no cases of fetal asphyxia even though vinbarbital sodium was administered within a very short time prior to delivery. After experience with the drug had reached considerable proportions, amnesia was induced deliberately with vinbarbital sodium in a number of patients who were known to be within minutes of delivery. In no instance was asphyxia or delayed respiration noted and 8 of these patients delivered in thirty minutes or less (2 at nineteen and seventeen minutes respectively) following the administration of vinbarbital sodium.

The pertinent details of the case histories of the 296 patients presented in this report are as follows: There were 183 primiparas or 61.8 per cent, and 113 multiparas or 38.2 per cent. In 284 patients (95.9 per cent) delivery was completed within twelve hours subsequent to induction of amnesia. Delivered from this group of patients (296 mothers) were 285 living infants (1 pair of twins). In addition there were 5 fetuses of two to five months intrauterine age, 3 monstrosities and 2 macerated stillborn infants of seven and eight months respectively. There were also 2 full-term stillborn infants delivered; one from a mother whose diabetes mellitus had been difficult to control throughout pregnancy and who died shortly after parturition; and one from a mother who had an unusually difficult labor of one hundred ten hours and in whom a cesarian section or other operative intervention was contraindicated. In the group of 285 living infants, there were 3 who were born prematurely. A conservative estimate of their average intrauterine age was approximately seven months. These infants were delivered two, four and a half and five and three-quarter hours respectively, subsequent to induction of amnesia with the intravenous preparation of vinbarbital sodium. There was no delay in establishment of respiration.

In this group also there were 8 living infants delivered by means of cesarean section. One child was delivered in this manner fifty-two minutes after vinbarbital sodium was administered to the mother. The time between administration of the drug and the delivery of the remaining 7 infants ranged from three to nineteen and a half hours. No deleterious effect attributable to the drug was noted in the mothers or infants.

In Group I, fifty-one mothers completed the second stage of labor within one hour of administration of vinbarbital sodium intravenously. Of these 21 were primiparas and 30 were multiparas.

Forty-eight living infants were delivered in this group among which are included one child delivered by cesarean section and a pair of twins delivered through the natural birth canal. There were 2 macerated stillborn infants whose intrauterine ages were calculated at seven and eight months respectively, and also 2 monstrosities.

In Group II, the second stage of labor was completed by 60 mothers in less than two hours, but more than one hour, after intravenous administration of vinbarbital sodium. Of these 25 were primiparas and 35 were multiparas. Sixty living infants were delivered in this group of which 1 child was born prematurely at approximately seven months.

In Group III, 70 mothers completed the second stage of labor in less than four, but more than two hours, after the intravenous dose of vinbarbital sodium. Of these 40 were primiparas and 30 were multiparas. Sixty-eight living infants were delivered among which are included 2 delivered by cesarian section. Two mothers delivered fetuses of approximately two and a half to three months intrauterine age.

The remainder of the series of 296 mothers, or 115 in Group IV, completed the second stage of labor four hours or more after vinbarbital sodium was administered intravenously. Only 12 mothers in this group failed to complete the second stage of labor within twelve hours. The average time of delivery of 103 mothers was approximately eight hours following intravenous administration of vinbarbital sodium. From this group of mothers 109 living infants were delivered among which are included 2 prematurely born babies of approximately six and a half to seven months intrauterine age and 5 infants delivered by caesarian section. There were 3 fetuses of two, four and five months respectively; one monstrosity and 2 full-term stillborn infants mentioned previously.

TABLE I. SUMMARY OF DATA

PATIENTS	ENTIRE SERIES	GROUP I*	GROUP II*	GROUP III*	GROUP IV*
Primiparas	183	21	25	40	97
Multiparas	113	30	35	30	18
Total	296	51	60	70	115
Living infants	285	48	60	68	109
Premature	3	-	1	-	2
Cesarean section	8	1	-	2	5
Stillborn	9	2	-	2	5
Monstrosities	3	2	-	-	1

\*Group I.—Delivery occurred one hour or less after induction of amnesia.

\*Group II.—Delivery occurred within two hours but more than one hour after induction of amnesia.

\*Group III.—Delivery occurred within four hours but more than two hours after induction of amnesia.

\*Group IV.—Delivery occurred four hours or more after induction of amnesia.

### Summary and Conclusions

1. Observations made on 1,500 consecutive patients and a study of the results obtained in the last 296 patients of this series, indicate that

vinbarbital sodium is an effective preparation for induction of obstetric amnesia and is without harmful effects to mother or child.

2. Complete amnesia was obtained in 90 per cent of the series of 1,500 consecutive patients to whom vinbarbital sodium was administered intravenously. Only 2 per cent of patients so treated failed to obtain amnesia and 8 per cent were able to recall isolated events.

3. Administration can be accomplished rapidly, and amnesia is obtained within ten minutes or less after injection.

4. In all instances patients were able to cooperate and respond to necessary requests during the course of labor. The induction of general anesthesia proceeded smoothly and did not precipitate any mental excitement or undue motor activity.

5. The contractility of the uterus was unaffected by vinbarbital sodium as evidenced by the following observations:

- a. There was no interruption or slowing of the progress of labor even when the drug was administered early.
- b. The incidence of post-partum hemorrhage was not increased over that usually encountered in this area.

6. No alteration in the vital functions of mother or child was observed during the first stage of labor regardless of the interval of time between administration of the drug and the onset of the second stage.

7. No mental depression was observed after delivery. The patient awakened from a refreshing sleep with no disorientation or "hangover."

8. In the entire series there was no case of fetal asphyxia or fetal death that could be attributed to the effects of the drug.

9. The intravenous use of vinbarbital sodium in this large series of cases has proved to be a most satisfactory preparation for induction of obstetric amnesia and has been found to meet all the requirements demanded of any drug employed for this purpose as set forth at the beginning of this presentation.

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## CONGENITAL VAGINAL OCCLUSION OF THE CERVIX\*

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TWO years ago a young woman presented herself because of sterility and incidental menorrhagia. On examination there was an apparent congenital absence of the cervix with an imperforate vaginal vault, which from the embryological viewpoint seemed to be an impossible malformation. Recently a second patient, who consulted me because of severe dysmenorrhea, was found to have essentially the same developmental defect. These two cases had so many similar features that it seems logical to discuss them together.

CASE 1.—R. S., aged 21 years, consulted me in January, 1942. She began menstruating at 13, and always had a painless and regular flow, lasting from eight to ten days. She had been married for two years and complained chiefly of sterility and frigidity, although during the previous few months there had been a little postmenstrual staining. The external genitals were normal. The configuration and size of the vagina were normal except for the apparent absence of the portio of the cervix in the vaginal vault. This area looked as though the patient had been subjected to a total hysterectomy. On bimanual examination a small uterus, deviated to the right, with normal adnexa could be palpated in the pelvis. After putting the vaginal vault on the stretch with a bivalve speculum, and making a careful search, a small pin-point opening in the center of the vaginal vault was seen (Fig. 1). This was not large enough to accept an ordinary uterine sound, nor even a fine wire probe. A bougie tip No. 5 ureteral catheter was then inserted through this small opening but was arrested at 3 cm. One week later I cut off the end of this catheter, reinserted it through the tiny opening, and took a series of salpingograms, using fractional injections of lipiodol, as suggested by Hyams. These pictures revealed an apparent pocket just above the vaginal vault, with a small diverticulum on each side, above which there was a dilated cervical canal and a small dextroverted uterus (Figs. 2 and 3). The contrast medium failed to demonstrate any tubal patency on the right side, but showed a long tube on the left side with apparent retention of the oil in the fimbriated extremity. The twenty-four-hour picture, however, demonstrated small flecks of oil scattered in the pelvis, so it was evident that the tube on the left side was open (Fig. 4). Five months later I attempted to circumcize the vaginal vault and mobilize the cervix, but after completing this operation was entirely dissatisfied with the end result, as I had not been able to find any anatomic landmarks or definite lines of cleavage. Four months after this plastic procedure, in October, 1942, the patient became pregnant and went through a normal pregnancy under the supervision of her family

\*Read at a meeting of the New York Obstetrical Society, February 8, 1944.

physician. She was delivered of a seven-pound baby by a general surgeon, who did a classical cesarean section in August, 1943, and had a smooth post-partum convalescence. When I re-examined this patient two months later, the vaginal vault still presented much the same appearance

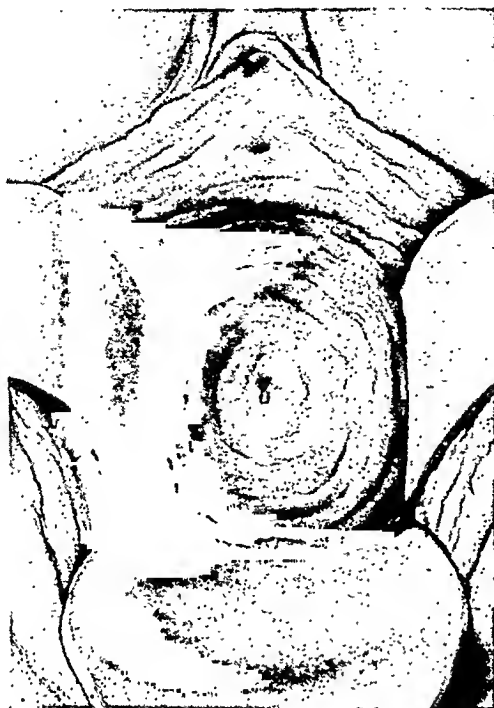


Fig. 1.—(Case 1.) Apparent congenital absence of the cervix, with small opening in the center of the vaginal vault.



Fig. 2.—(Case 1.) Injection of 2 c.c. of lipiodol, showing a pocket between the vagina and cervix with a small diverticulum on each side.

as when she was first seen, except for the fact that the epithelial covering of the area in which the cervix normally lies looked much like the surface of a cervix which had been subjected to a partial amputation. There was just a little difference in the smoothness of the mucous membrane covering this area contrasted with the rugae in the rest of the vaginal canal.



Fig. 3.—(Case 1.) Injection of 10 c.c. of lipiodol, showing the rugae in the dilated cervical canal, marked dextroversion of the uterus, right tubal occlusion at the uterine cornu, and apparent tubal occlusion of the left tube at the fimbriated extremity.



Fig. 4.—(Case 1.) Twenty-four hours after lipiodol injection, showing flecks of contrast medium in the left iliac fossa, indicating patency of the left tube.

Unfortunately, this patient could not be persuaded to submit to additional salpingograms after delivery.

CASE 2.—J. R., aged 22 years, consulted me in August, 1943, because of severe and increasing dysmenorrhea, with slight menorrhagia. She began menstruating at 11, and usually flowed rather profusely for six days, at two-week intervals. While there had always been some pain with the flow, the dysmenorrhea had been increasing in recent months. She had been married for a year and a half before seeking medical advice. On examination this patient's vaginal vault was found to resemble exactly the one described in the first case, except for the fact that no opening could be found in the midline. After prolonged search, a tiny opening was found far over on the left side (Fig. 5).

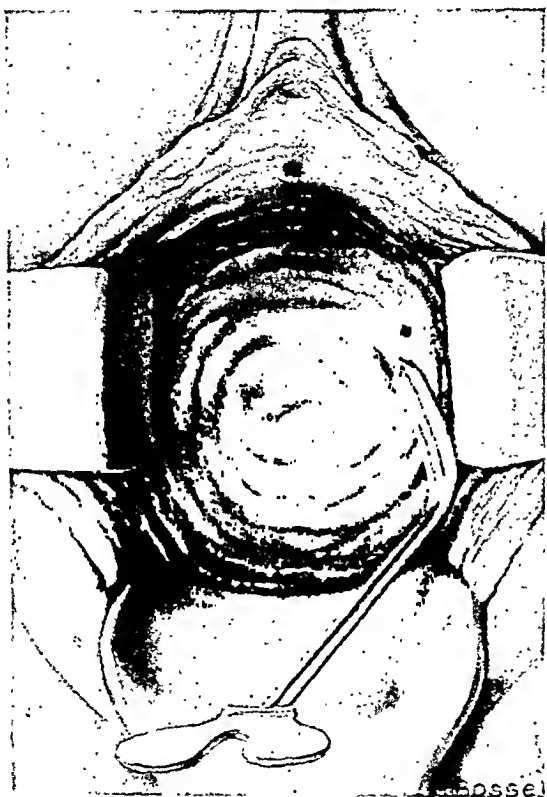


Fig. 5.—(Case 2.) Grooved director pointing to small aperture in left side of the vaginal vault.

This aperture accepted an ordinary silver probe without difficulty. The probe could be inserted for about seven cm., and could be moved around to a certain extent. On bimanual examination a cervix and uterine corpus could be palpated in the midline, with a normal tube and ovary on each side. Salpingograms in this instance, which were also made by using a ureteral catheter tip, disclosed a large blind pouch only, and none of the contrast medium entered the cervical canal, uterine cavity, or tubal lumina (Figs. 6 and 7). In October, 1943, a malleable grooved director was inserted into the opening with its tip curved to the right and the mucous membrane of the vaginal vault was split transversely with a knife blade on the grooved director (Fig. 8). The tissue, which was cut through by the knife blade, looked like normal vaginal





Fig. 6.—(Case 2.) Injection of 2 c.c. of lipiodol, demonstrating large supravaginal pocket.



Fig. 7.—(Case 2.) Injection of 10 c.c. of lipiodol, distending the pocket and disclosing no evidence of a uterus.

mucous membrane of average thickness and, as the incision was made, the margins retracted anteriorly and posteriorly, permitting the escape of a large quantity of gelatinous mucus, with delivery of a fully-developed cervix into the vagina (Fig. 9). The cervix was normal in every respect except for a large area of erosion surrounding the external

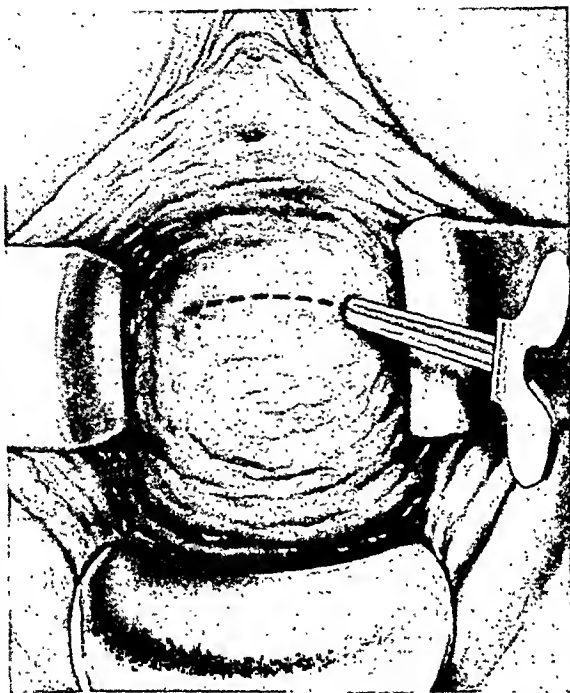


Fig. 8.—(Case 2.) Showing line of transverse incision of vaginal vault mucous membrane.



Fig. 9.—(Case 2.) Exposure of normal cervix after incision.

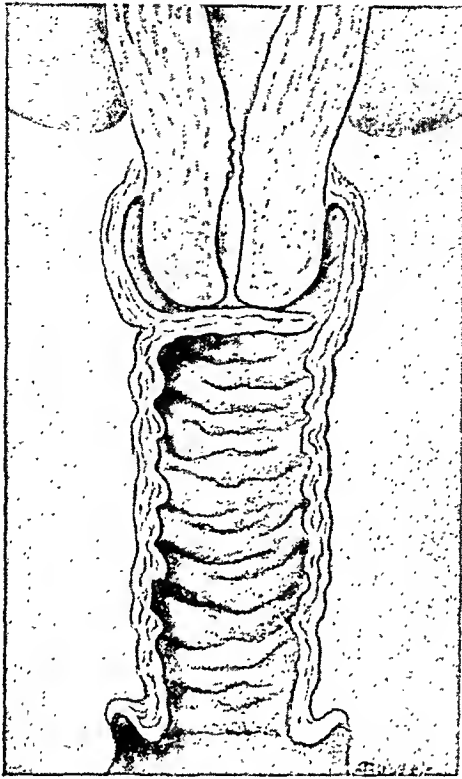


Fig. 10.—(Case 2.) Diagrammatic depiction of the uterovaginal anomaly.



Fig. 11.—(Case 2.) Salpingograms taken 2 months after operation, demonstrating a normal uterus and tubal patency.

os. A uterine sound was easily inserted into the uterus for a distance of three inches, and the endometrial surface was curetted with a semisharp curette. It then became evident that this patient had a normal uterus and adnexa, but that the cervix had been completely occluded by a transverse partition of vaginal mucous membrane (Fig. 10). After two normal and painless menstrual periods following the operation, another series of salpingograms was made, by injecting lipiodol through a cannula inserted into the newly exposed cervix. These pictures demonstrated a well-developed uterus and bilateral tubal patency (Fig. 11).

### Comment

The first mysterious feature of these two cases is the developmental origin of the transverse occluding membrane in the upper vagina which concealed the cervix. How the Müllerian duct development was distorted to create the occluding transverse partition in the vaginal fornix is an enigma. Robert Meyer believes that most vaginal occlusions at the introitus are acquired by inflammatory processes presumably caused by infectious diseases of childhood. Perhaps this theory could be accepted in the first case, but it hardly seems applicable in the second one, because the vaginal vault tissue was too thick and in no wise differed from the rest of the vaginal mucosa. The second peculiarity which is difficult to explain in both cases is the presence of the miniature openings in the obstructing partitions, one in the center and one far on the left side. They had no direct continuity with the cervical canal in either instance, yet provided a means of egress for mucus and menstrual blood through the false pouch between the cervix and vagina. The original salpingograms demonstrated that the ureteral catheter tip did not enter the cervical canal in either patient, and the filling of the endometrial cavity in the first case seems to have been due to little more than good fortune. The subsequent pregnancy was an agreeable surprise, especially because of the tubal occlusion on one side and questionable patency on the other. It is a matter of regret that the operator did not do a low flap section, which would have permitted inspection of the cervical region after detachment of the bladder.

The disclosures revealed by the operation in the second case were helpful in formulating a clearer conception of the anatomic peculiarities of both patients. The end results of the two surgical procedures may be regarded as satisfactory, since the sterility was overcome in the first instance, and the dysmenorrhea completely relieved in the second.

580 PARK AVENUE

### Discussion

DR. I. C. RUBIN.—In a fairly large experience with sterile women I have encountered various degrees of what I have called cervical phimosis, of which the second case of Dr. Dannreuther's is more particularly representative than the first case. In this condition there is a constriction of the vagina in front of the cervix, which varies from a diameter through which you can put your index finger to one which will admit only a lead pencil. The most extreme degree of vaginal phimosis is,

I believe, represented by Dr. Dannreuther's first case. I recently had a case which was the exact counterpart of his. This patient was also seen by Dr. Paul Titus of Pittsburgh who agreed as to the findings. The external os was just a tiny point in the center of a flat vaginal vault. By a sort of discission operation a new vaginal portion of the cervix was formed. I dilated the cervical canal and packed petroleum jelly gauze into the denuded area representing the fornices and also inserted a gauze packing into the newly dilated cervical canal. A uterotubal insufflation done subsequently demonstrated tubal patency. The patient became pregnant six months later, went through a normal pregnancy and was given the test of labor. Unfortunately, the membranes ruptured prematurely. The cervix did not dilate satisfactorily so that after 36 hours, a cesarean section was done. Mother and baby did well.

In Dr. Dannreuther's case the patient was very fortunate because she became pregnant despite the fact that one tube was closed and the other open and lipiodol had been used.

These cases are not frequent, but they are not rare. The rarest type of cervical phimosi, I think, are the two varieties which Dr. Dannreuther has presented.

DR. DANNREUTHER (closing).—Perhaps cervical phimosi is a better term for the peculiar anomalies in these cases. It is comforting to know that Dr. Rubin was as dissatisfied with the end result in his attempted plastic procedure, as I was with mine in my first case.

## VESICAL AND RECTAL INCONTINENCE IN THE SAME PATIENT\*

### Complete Laceration of the Perineum Following Childbirth and Large Vesicovaginal Fistula Following Abdominal Panhysterectomy

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*(From the Carney Hospital)*

ON ADMISSION to the Carney Hospital on April 17, 1941, Mrs. L. J., a 49-year-old white woman complained of constant urinary incontinence. Three years before admission, she had had an abdominal panhysterectomy in a neighboring city, and this was immediately followed by urinary incontinence. Two months later, an operation was performed in an attempt to close a vesicovaginal fistula, but this was unsuccessful. In November, 1940, a second operation was attempted, with the same result, and in February, 1941, she was operated upon for the third time and still had constant urinary leakage through the vagina. The hysterectomy and the three operations for vesicovaginal fistula had all been performed in the same city. She was then referred to Dr. Roger C. Graves, Urologist-in-chief at the Carney Hospital for the transplantation of the ureters in the sigmoid. She had had no serious illnesses and no other operations. Menstruation was established at the age of 15, she had a 28- to 30-day cycle, the flow, which lasted from 3 to 4 days, was moderate in amount. She had had a surgical menopause three years previously. She had had five children who were all living and well, and no miscarriages. The only significant feature in her family history was that her mother had died of carcinoma of the stomach at the age of 75 years.

#### Examination

The physical examination revealed a woman small in stature, poorly developed and poorly nourished. The blood pressure was 120 systolic and 80 diastolic. The head and neck showed no gross abnormalities. The chest was symmetrical, the lungs were resonant and clear throughout and the heart, which was not enlarged, presented sounds of good quality; the rate was normal, the rhythm was regular, and there were no murmurs. The abdomen was thin and relaxed; the liver and spleen were not felt; there were no masses or areas of tenderness; there was a well-healed median pelvic incision. The vaginal examination revealed that the vulva, urethra and vulvovaginal glands were normal in development. The external genitals were excoriated, incrustated with urinary salts and the surface of the skin bled readily when touched with a gauze sponge. The perineum had been lacerated through the sphincter ani and the ends of the sphincter muscle were retracted laterally. There was no cystocele. The uterus had been completely removed with the adnexa. The vaginal vault showed marked scarring as the result of the four previous operations. At the summit of the vault there existed a vesicovaginal fistula which readily admitted the tip of the examining finger. A cystoscopic examination, performed by Dr. Graves, disclosed that the opening of the left ureter was in close proximity to the fistula while the opening of the right ureter was some distance away from it. After examination it was evident that if the ureters were transplanted

\*Read at a meeting of the Obstetrical Society of Boston, January 18, 1944.

in the sigmoid that the urine would emerge from the rectum as it did from the vagina, since there was no anal sphincter to hold back the urinary flow. Two alternatives presented themselves: the first, closure of the vesicovaginal fistula through the vagina, the consultants believing that this could be accomplished; and the second, the reconstruction of the anal sphincter, the repair of the perineum, and, subsequently, the transplantation of the ureters in the sigmoid. The first course was decided upon and the patient was transferred to me.

### Treatment

During the fourteen days which elapsed between April 17, and May 1, 1941, when the patient was operated on, she was kept in bed, the external genitals were irrigated with mild, warm acetic acid solution to dissolve the urinary salts incrustated on the skin, and the skin was covered by diachylon paste. At the end of April the parts were healed.

### Operation on the Vesicovaginal Fistula

Under gas-oxygen, ether anesthesia, the external genitals and vagina were prepared with tincture of zephiran. A tight gauze pack was introduced in the vagina in an attempt to plug the hole in the bladder which was filled with sterile water. Dr. Graves passed a cystoscope and introduced a catheter in the left ureter in order to identify it while closing the fistula; the ureteral opening was found to be about 1 cm. away from the fistula. The fistula was in the vaginal vault, directed to the left and about 2 cm. in circumference. An incision was made in the scar tissue around the fistulous opening close to its edge, the vaginal wall was dissected away from the opening in all directions and it was possible to freely mobilize the bladder. The opening in the bladder was closed in a transverse direction with a running suture of No. 0 chromic catgut, using due care that the suture did not penetrate into the bladder. There was left a safe margin between the left end of the closed fistula and the catheter in the left ureter. This suture line in the bladder was reinforced by a series of No. 00 chromic catgut, interrupted sutures placed in the bladder muscularis. The bladder was tightly closed. The vagina was closed in a longitudinal direction in order to stagger the suture lines, using eleven interrupted sutures of No. 30 alloy wire, the ends of these sutures being arrested by lead shots. A plain No. 16 French, male soft rubber catheter, was introduced through the urethra and was attached to the right thigh. A small amount of bloody urine which had accumulated in the bladder was obtained. The patient was returned to bed in satisfactory condition. The ureteral catheter was left in and removed after 53 hours.

On May 17, 1941, since there had been no leaking of urine for 17 days, the patient was placed on an examining table in order to remove the metallic sutures. She was a very uncooperative, nervous, restless person. The first five sutures were removed without difficulty; while removing the sixth, she suddenly pulled up on the table so that the suture loop cut through the anterior vaginal wall. This was followed by the escape of a few drops of urine. She was put back to bed, constant drainage was re-established and I learned the lesson that these sutures should be removed under anesthesia. The small opening in the vaginal wall readily healed, and in a few days the catheter was removed and the patient was allowed out of bed, with a healed bladder. She had no difficulty in voiding from then on.

### Operation for the Complete Laceration of the Perineum

On July 15, 1941, the patient was taken to the operating room; general anesthesia was administered, and the external genitals and vagina were prepared with tincture of zephiran. The remaining alloy wire sutures were readily removed; the bladder was well healed. The complete tear of the perineum was repaired, using the layer method. No. 0 and No. 00 chromic catgut were used throughout. One suture of prepared silk was passed through the skin and the united ends of the sphincter ani muscle to act as a splinting stitch. The primary result was entirely satisfactory.

Nine days after operation, the edges of the incision separated completely, there had been no infection, but the tissues had failed to heal.

The patient was again taken to the operating room on July 20, 1941, where general anesthesia was administered and the genitals were prepared as previously. The levator ani muscles were completely separated, the sphincter ends had separated despite the fact that the silk splinting stitch was still in place, but the vaginal part of the incision had completely healed. The edges of the separated incision were trimmed and curetted. The ends of the sphincter ani muscle were approximated by one interrupted suture of No. 2 forty-day chromic catgut. The edges of the levator ani muscles were approximated with a few interrupted sutures of the same material, and the rest of the perineum was closed with interrupted No. 30 alloy wire sutures, loosely tied. During her convalescence she was given large doses of vitamin C. At the end of two weeks the metallic sutures had been removed, the sphincter was healed, the perineum was healed except for a small area at the midpoint which was filling in rapidly, and she had good bowel control.

She was seen at the office on August 15, 1941, and a small granulating area at the middle of the perineum was discovered. On September 22, 1941, the perineum was almost completely healed, and gave good support. The sphincter was well healed. She was seen again on October 24, and November 7, 1941. On the last visit the following note was made: "The perineum is entirely healed and gives good support; the anus is well healed; she has satisfactory bowel control; The vesicovaginal fistula is tightly closed." The findings on December 5, 1941, were the same as on November 7, 1941, and the patient was discharged cured.

### Summary

A small, poorly developed, and poorly nourished, 49-year-old woman, the mother of five children, was referred to the Carney Hospital on April 17, 1941. She had had a complete laceration of the perineum at the birth of her first child. Three years before admission she had had an abdominal panhysterectomy and double salpingo-oophorectomy. The bladder was injured at operation with a resultant vesicovaginal fistula. Three operations had been done, without success, to close this vesicovaginal fistula before her admission. The vesicovaginal fistula was closed through the vagina by means of alloy wire sutures. Subsequently the complete tear of the perineum was repaired. At the end of 9 days the perineal tissues had completely separated; no infection was present. The perineum was again sutured with alloy wire sutures. She was given large doses of vitamin C and the sphincter ani muscle and perineal body healed after the second operation. She was discharged with a healed bladder, voiding normally, with a healed sphincter ani and perineal body and with satisfactory bowel control.



## ONE-DAY SULFONAMIDE TREATMENT OF CHRONIC GONORRHEA IN THE FEMALE

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THE revelation by Dees and Colston and by Reuter in May, 1937, that sulfanilamide is effective in the cure of gonorrhea, initiated many experiments in the sulfonamide treatment of this disease. The dosage schemes originally proposed were modified by others and the period of treatment abbreviated in various clinics. Marked variations in the reported results of this treatment could be ascribed to differences in the dosage, in duration of administration, and in the criteria of cure. The substitution first of sulfapyridine, then of sulfathiazole, sulfadiazine, and other compounds, has further complicated the picture. Sulfanilamide and sulfapyridine have now been displaced in the treatment of gonorrhea by the newer preparations because of their lessened toxicity and greater therapeutic effectiveness. With sulfathiazole and sulfadiazine too, there is variation in the recommended dosages and periods of administration. Some advise a ten-day course, while others have found five or seven days of treatment equally effective.

In previous reports on the treatment of gonorrhea in the female with sulfanilamide or sulfapyridine, we<sup>1, 2</sup> noted that patients given either drug, whose treatment was stopped on the second to the fifth day because of some toxic reaction, were cured of gonorrhea in as high a proportion as those who continued with the medication for two weeks. Douglas<sup>3</sup> has observed that gonococci disappear from the secretions within four to six hours after the beginning of sulfadiazine medication. At his suggestion, and at the suggestion of Mahoney and Van Slyke, we undertook to investigate the effect of the administration of sulfadiazine or of sulfathiazole during one day to a group of women all with cultures positive for the gonococcus.

The influence of war economy, taxing the nursing as well as the medical personnel and hospital administration, caused us to eagerly undertake this one-day treatment of gonorrhea. Prolonged medication may predispose to sensitivity and by limiting the administration of the drug to one day, we hoped to avoid this possible sensitization.

Beginning in January, 1943, patients sent into our service at the Kingston Avenue Hospital with a culture report positive for the gonococcus, were given sulfonamide medication routinely for only one day.

A few patients, because of poor general condition, profound anemia, poor kidney function, or a history of intolerance to sulfonamides, were treated by other methods and are not included in this study. A complete history, physical and gynecological examination, complete blood count, and urine analysis, were first recorded. Patients were confined to the hospital but were ambulatory. They were on a general hospital diet. Fluids were forced before, during and after chemotherapy, the average intake was over 2,000 c.c. The day preceding the administration of the sulfonamide, each patient was given 32 grams of sodium bicarbonate.

The first group of patients (Group A) was given sulfadiazine 6 grams, during a single day—half at 9 A.M. and the other half at 3 P.M. An equal amount of sodium bicarbonate was administered at the same time.

TABLE I. GENERAL DATA ON ALL PATIENTS

	SULFADIAZINE		SULFATHIAZOLE
	GROUP A 6 GM.	GROUP B 8 GM.	GROUP C 8 GM.
No. Patients	96	97	88
Colored	59	61	54
White	37	36	34
Gonorrhea (alone)	76	83	66
Gonorrhea and syphilis	20	14	22
Age—Average	27 years	25.5 years	25.2 years
Oldest	44	47	49
Youngest	18	16	16
Weight—Average	133.3 pounds	127.3 pounds	131 pounds
Highest	300	187	338
Lowest	88	87	95
Colored (average)	132.1	124.2	132.0
White (average)	135.7	133.0	129.5

The second group (Group B) was treated identically except that 8 grams of sulfadiazine were administered during one day.

TABLE II. CLINICAL EXAMINATION BEFORE TREATMENT

	SULFADIAZINE		SULFATHIAZOLE
	GROUP A 6 GM.	GROUP B 8 GM.	GROUP C 8 GM.
Urethritis	46 patients	34 patients	30 patients
Skenitis	22	19	14
Bartholinitis	5	9	8
Cervical discharge			
scant	27	34	10
moderate	28	27	27
profuse	24	29	38
very profuse	17	7	5
Cervical erosions	36	27	21
Adnexal thickening	56	38	29
Adnexal masses	9	14	22
Adnexa negative	31	45	37

The third group (Group C) was given 8 grams of sulfathiazole in exactly the same fashion.

TABLE III. BACTERIOLOGIC FINDINGS ON ADMISSION  
(REPORTED BY HEALTH DEPT.)

	SULFADIAZINE		SULFATHIAZOLE
	GROUP A 6 GM.	GROUP B 8 GM.	GROUP C 8 GM.
Culture +, smear +	13	15	26
Culture +, smear negative	80	71	58
Culture +, smear suspicious	3	11	4
	96	97	88

TABLE IV. NUMBER OF POSTTREATMENT CULTURES IN "CURED" CASES

	SULFADIAZINE		SULFATHIAZOLE
	GROUP A 6 GM.	GROUP B 8 GM.	GROUP C 8 GM.
Average number of cultures in all "cured" cases	5.4 culture	5.4 culture	4.1 culture
Average number of cultures in gonorrhea cases	5.1	5.3	4.1
Average number of cultures in gonorrhea and syphilis cases	6.5	5.7	4.1
Discharged after 2 cultures	1 patient	1 patient	0 patient
Discharged after 3 cultures	3	6	3
Discharged after 4 cultures	13	6	41
Discharged after 5 cultures	29	25	22
Discharged after 6 cultures	17	32	10
Discharged after 7 cultures	14	7	0
Discharged after 8 cultures	3	4	0
Discharged after 9 cultures	1	0	0
	81	81	76

TABLE V. FAILURES\*—BACTERIOLOGIC FINDINGS

GROUP A SULFADIAZINE 6 GM.				GROUP B SULFADIAZINE 8 GM.			GROUP C SULFATHIAZOLE 8 GM.		

\*Including suspicious smears.

In all cases cultures and spreads were taken from the urethra and cervix (Skene's and Bartholin's, when indicated) the day following treatment and once or twice weekly during their hospital stay. The patients were examined gynecologically each week by the resident staff and also by the visiting staff working independently. The period of observation following chemotherapy averaged 30 days.

TABLE VI. FAILURES—DIVIDED INTO THREE GROUPS

	TOTAL NUMBER TREATED	FAILURES						CULTURE NEGATIVE				CULTURE POSITIVE			
		POSITIVE CULTURE		POSITIVE SMEAR		POSITIVE CULTURE OR SMEAR		SMEAR		SUSPICIOUS		OR SMEAR OR SUS- PICIOUS SMEAR		POSITIVE CULTURE	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Group A (6 Gm. sulfadiazine)	96	7	7.3	2	2.1	9	9.4	6	6.2	15	15.6				
Group B (8 Gm. sulfadiazine)	97	11	11.3	2	2.1	13	13.4	3	3.1	16	16.5				
Group C (8 Gm. sulfathiazole)	88	6	6.8	2	2.3	8	9.1	4	4.5	12	13.7				
Group A—Gonorrhea alone	76	7	9.2	2	2.6	9	11.8	5	6.6	14	18.4				
Group A—Gonorrhea plus syphilis	20	-	0	-	0	0	0	1	5.0	1	5.0				
Group B—Gonorrhea alone	83	11	13.3	2	2.3	13	15.6	2	2.4	15	18.0				
Group B—Gonorrhea plus syphilis	14	-	0	-	0	0	0	1	7.1	1	7.1				
Group C—Gonorrhea alone	66	4	6.1	2	3.0	6	9.1	1	1.5	7	10.6				
Group C—Gonorrhea plus syphilis	22	2	9.1	-	0	2	9.1	3	13.6	5	22.7				
Group A—Colored patients	59	3	5.1	-	0	3	5.1	2	3.4	5	8.5				
Group A—White patients	37	4	10.8	2	5.4	6	16.2	4	10.8	10	28.0				
Group B—Colored patients	61	2	3.3	-	0	2	3.3	2	3.3	4	6.5				
Group B—White patients	36	9	25.0	2	5.6	11	30.6	1	2.8	12	33.4				
Group C—Colored patients	54	1	1.9	1	1.8	2	3.7	4	7.4	6	11.1				
Group C—White patients	34	5	14.7	1	2.9	6	17.6	-	0	6	17.6				

## Results

In Table VI we see that the failures proved by positive smear or culture were 9.4 per cent in Group A, 13.4 per cent in Group B and 9.1 per cent in Group C. There is no appreciable difference in effectiveness between sulfadiazine and sulfathiazole as used in this study. In each of the groups the percentage of patients with persistently positive smears and cultures was much larger among the white than among the colored patients (Group A—5.1 per cent colored vs. 16.2 per cent white); [Group B—3.3 per cent colored vs. 30.6 per cent white]; (Group C—3.7 per cent colored vs. 17.6 per cent white).

It had previously been observed that patients under treatment for both syphilis and gonorrhea had fewer failures than those with gonorrhea alone. In Table VI we find this difference very striking. In Groups A and B there were no failures among the syphilis plus gonorrhea cases, whereas in the gonorrheal cases of Group A failures were 11.8 per cent and in Group B 15.6 per cent. In Group C, however, there was no such difference.

From Table VII we find that the percentage of failures by smear and culture of all colored patients in the three groups combined was 4.1 per cent whereas the whites failed in 20.9 per cent. Colored patients of all three groups treated for gonorrhea alone failed in 5.8 per cent, while whites failed in 21.0 per cent.

TABLE VII. FAILURES, THREE GROUPS COMBINED, RACIAL DIFFERENCES

	NUMBER TREATED	FAILURES				POSITIVE CULTURE OR SMEAR, OR SUSPICIOUS	
		POSITIVE CULTURE ALONE		POSITIVE CULTURE OR SMEAR			
		NUM- BER	%	NUM- BER	%	NUM- BER	%
Colored patients	171	6	3.5	7	4.1	15	8.8
White patients	110	18	16.39	23	20.9	28	25.5
Gonorrhea alone, all races	225	22	9.8	28	12.0	36	16.0
Gonorrhea plus syphilis, all races	56	2	3.6	2	3.6	7	12.5
Gonorrhea alone, colored	125	6	4.8	7	5.8	11	8.8
Gonorrhea alone, white	100	16	16.0	21	21.0	25	25.0
Gonorrhea plus syphilis, colored	46	0	0.0	0	0.0	4	8.7
Gonorrhea plus syphilis, white	10	2	20.0	2	20.0	3	30.0

Considering the white patients, those treated for gonorrhea alone failed in 21.0 per cent while those treated for syphilis and gonorrhea failed in 20 per cent. Among the 46 colored patients treated for both gonorrhea and syphilis there was not a single positive smear or culture after treatment, whereas among the colored treated for gonorrhea only 5.1 per cent had a positive smear or culture after treatment. There is therefore not only a considerable difference in failures between the races, but there seems to be in the colored race an improvement of the results as a consequence of the coincidental antisyphilitic treatment.

In Table VIII it is seen that in Groups A and B (sulfadiazine cases) the failures weighed an average of 15.5 and 13.7 pounds more respectively than the average of their group. In Group C there was no significant difference in weight.

TABLE VIII. AGE AND WEIGHT OF FAILURES COMPARED WITH ALL CASES TREATED

	GROUP A	GROUP B	GROUP C
Average age of failures	27.1 years	25 years	23.7 years
Average age, all cases	27.0	25.5	25.2
Average weight of failures	148.8 pounds	141.0 pounds	128.0 pounds
Average weight of all cases	133.3	127.3	131.0
Average weight of white failures	160.6	142.7	130.8
Average weight of white, all cases	135.7	133.0	129.5
Average weight of colored failures	134.5	137.8	124.1
Average weight of colored, all cases	132.1	124.2	132.0

In none of the three groups was age a factor.

In Table IX the cure rates in the three groups are listed. The cases with suspicious smear reports and negative cultures constitute a doubtful category, which we have listed as failures in the upper part of the Table, for the sake of conservatism in the interpretation of results. For practical purposes and for comparison with other reported series, this group with suspicious smears is ignored and results are based only upon positive smear or culture reports.

TABLE IX. ANALYSIS OF CURES, DIVIDED INTO THREE GROUPS

	SULFADIAZINE				SULFATHIAZOLE	
	GROUP A 6 GM.		GROUP B 8 GM.		GROUP C 8 GM.	
	TOTAL NO.	%	TOTAL NO.	%	TOTAL NO.	%
Total number patients treated	96		97		88	
Including suspicious smears						
Failures	15	15.6	16	16.5	12	13.6
Cures	81	84.4	81	83.5	76	86.4
Excluding suspicious smears						
Failures (positive smear or culture)	9	9.4	13	13.4	8	9.1
Cures	87	90.6	84	86.6	80	90.9

Major toxic symptoms were not observed in this series of cases. The average concentration of sulfadiazine in blood taken three hours after the last dose in 36 patients of Group A was 4.2 mg. per cent, while it averaged 6.0 mg. per cent in 72 patients in Group B.

Most of the failures following the one-day treatment had a week of rest, then were given four grams of sulfathiazole daily for seven days. We had previously found that sulfathiazole four grams daily for seven days gave us a 95.0 per cent cure rate. This sulfathiazole course rendered most of them bacteriologically negative.

## Summary

Three groups of hospitalized women with chronic gonorrhea, proved in every case by a positive culture, were treated by means of sulfadiazine or sulfathiazole administered during one day. Methods of follow-up and technique of bacteriologic examination were unchanged.

The percentage of bacteriologic failures differed little in the three groups. Major toxic manifestations were absent. Age of the failures did not differ significantly from the average in each group. With sulfadiazine the average weight of the failures was 14 to 15 pounds greater than the average weight of all the patients treated with this drug. With sulfathiazole there was little difference in weight between the failures and the entire sulfathiazole group.

There was a definite racial difference in results, the failures in the white patients being three to four times greater than in the colored. This observation had previously and independently been made by others.<sup>5, 6</sup> In the colored the coincidental treatment of syphilis seems to improve the results of the treatment of gonorrhea. We do not know whether the better therapeutic results of the colored patients treated for gonorrhea with sulfonamides is due to a superior racial immunologic response, or to better reaction to the sulfonamides due to the pigmentation of the skin.

## Conclusions

The administration of sulfadiazine or sulfathiazole during a single day to hospitalized women with cultures positive for the gonococcus was followed by the disappearance of gonococci in 86.6 per cent to 90.9 per cent of the cases. There was no significant difference of results following 8 Gm. sulfathiazole, 8 Gm. sulfadiazine or 6 Gm. sulfadiazine. There was a difference in response of patients of the colored and white races, the failures being three to four times greater in the whites.

We are not ready to advocate the general use of the "one-day treatment" of gonorrhea and believe that it should be used only in hospitalized patients when time is at a premium.

The laboratory part of this study was conducted under the supervision of Dr. Philip Rosenblatt to whom we hereby express our thanks.

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## TORSION OF OVARIAN CYSTS IN CHILDREN

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THE rarity of ovarian cysts with torsion of the pedicle in children justifies the report of the following two cases which occurred recently. Through 1925 a total of 99 cases of ovarian cysts in children had been reported in the American and English literature,<sup>1</sup> over 50 per cent of these being in children approaching puberty.<sup>2</sup> Out of 12,260 admissions to the Boston Children's Hospital in 1929, there was reported by Lanman only one torsion of an ovarian cyst and this in an older child.<sup>3</sup> Since the opening of the Fayetteville City Hospital in 1912, there has been only one case of torsion of an ovarian cyst in a child under five years of age, and, since July 1, 1930, only one case of an ovarian cyst with a twisted pedicle in a child of twelve years. There was one twelve-year-old girl with hydrosalpinx and a small cystic right ovary with torsion of the tube, and a fourteen-year-old child with a ruptured right ovarian cyst without torsion.

CASE 1.—The following case occurred in a four-year-old white female child. The child had been perfectly well. On July 30, 1943, she ate her usual breakfast about 7:30 A.M. Shortly afterwards she went to stool and immediately cried out in pain. She vomited her breakfast and nausea followed. The nausea and vomiting continued throughout the day and night. The child ate nothing and lay quietly except when seized with pain, when she would lie on her abdomen, draw up her knees, and moan in what appeared to be paroxysms of abdominal pain.

The child had an attack of tonsillitis two weeks previously from which she quickly recovered without known ill effects. She was born February 10, 1939, the labor being a normal one of five hours' duration. She had been immunized for diphtheria at six months, pertussis at eight months, smallpox at nine months, one and one-half and two years, and typhoid at two years. She was said to have had occasional colds and attacks of tonsillitis in the past. Internal strabismus of the right eye was first noticed in February, 1942. Development was otherwise normal.

The family history was significant in that both the mother and maternal grandmother had ovarian cysts removed surgically.

On admission to the hospital, July 31, 1943, on the second day of illness, the symptoms continued unabated. The pain was not definitely localized, but seemed more intense around the umbilicus, and tenderness was chiefly on the right side at McBurney's point. The patient's blood count was as follows: red blood cells, 4,330,000, hemoglobin 70 per cent, leucocytes 10,480, eosinophiles 1, stabs 1, segmented 74, lymphocytes 23, and monocyte 1. Two later blood counts were made the same day, with little variation. The urinalysis showed: reaction 6.0, acid, specific gravity 1.040, albumin negative, sugar negative, occasional red blood cell, and occasional white blood cell. The following morning the child took some nourishment and seemed to be in better condition. The total leucocyte count was 11,900, with stabs 2, seg-



mented 83, and lymphocytes 15. Urinalysis showed: reaction 6.0, specific gravity 1.020, albumin faint trace, pus 3 to 5 per high power field, and no red blood cells. There were several paroxysms of severe abdominal pain during the day. A single bowel movement was loose, and no blood was present. The most commonly reported symptoms of torsion of ovarian cysts, frequency and dysuria, were not present. Rectal examination showed a movable mass in the midline about the size of a man's thumb. At noon the leucocyte count was 18,900, stabs 4, segmented 77, and lymphocytes 17. About midafternoon the leucocyte count was 13,900, stabs 4, segmented 66, lymphocytes 29, and monocyte 1. The differential diagnosis at this time was: (1) intussusception, (2) acute appendicitis, (3) pyelitis, (4) ovarian cyst. Three consultants saw the patient during the day. Surgery was not advised even though a mass could be felt and the differential count was elevated.

The child's pain continued during the night and she appeared more ill. Operation was performed on August 2. A lower midline abdominal incision was made, and abundant serosanguineous fluid was found in the peritoneal cavity. The right ovary and tube immediately presented in the wound, and were twisted on their pedicle three times. Both appeared gangrenous. The ovary was cystic, about five centimeters in diameter, and the tube enlarged in diameter about four times. Both were removed by ligating the pedicle and excising the tube and ovary. The raw surfaces were peritonealized with continuous Dulox suture. The left tube, and ovary and the uterus were normal. The appendix, which was bound down by adhesions and subacutely inflamed, was also removed, the stump being treated with carbolic acid and alcohol and inverted by means of a purse-string suture. The blood vessels on the right side appeared gangrenous up to the iliac crest. Closure was made without drainage.

The child made an uneventful recovery except for a small cutaneous abscess at the upper angle of the wound.

The following points are of interest in this case: Torsion probably occurred after defecation. There was no rigidity, no temperature, and the patient was not acutely ill. Following the acute onset, the patient took normal nourishment and had normal defecation. There was no abdominal distention. The pain occurred in paroxysms. A mass was present rectally in the midline.

While the preceding report was typical of an acute torsion, the following case was more subacute, or chronic in nature.

CASE 2.—This patient was first seen on April 1, 1942. She was a twelve-year-old girl whose chief presenting symptom was pain occurring in paroxysms in the lower left side of the abdomen. She was nauseated and vomited. The child's mother was a nurse and requested that she remain at home. She was admitted to the hospital the following day. Throughout the night the pain continued in paroxysms, some of which lasted as long as thirty-five minutes. The leucocyte count was 11,000, with eosinophiles 3, stabs 1, segmented 47, and lymphocytes 49. The urinalysis was negative. There was a fullness in the lower left quadrant with tenderness, but no rigidity. There had been no other illness of consequence, but for a year and a half previously, the child had complained of severe pain in the lower left side upon exertion. For the past six months there had been a thick dark vaginal discharge about every four weeks and at this time the pain was accentuated. The family history was irrelevant.

The patient stayed in the hospital four days and during this time the symptoms abated. She was discharged on April 7. About 5 A.M., April 9, the pain became much worse, and was associated with nausea. The leucocyte count at this time was not elevated. A mass about which there had been some doubt previously was now plainly felt in the lower left quadrant. The following day the mass seemed larger. The leucocyte count was elevated to 15,850, with segmented 76, and lymphocytes 24. Later the leucocyte count was 14,350 with 84 polymorphonuclears and 16 lymphocytes. The diagnosis was undetermined, but operation was advised. A midline incision was made, and bloody fluid was present in the abdominal cavity. A mass consisting of the left tube and ovary filled the greater part of the pelvis. The tube and ovary had been twisted several times, and the tube was gangrenous. The ovary was enlarged to about seven and one-half centimeters in diameter. A portion of the cyst, containing blood, was ruptured in untwisting the pedicle to liberate the mass. The left tube and ovary were clamped and excised. The stump was sutured with continuous 20-day number 2 catgut, and the raw surfaces were peritonealized. The appendix was normal, but was removed with inversion of the stump. Other organs were normal. Closure was in layers without drainage. The ovary consisted of a small cystic portion containing dark blood, and a solid portion which was a dermoid cyst containing four well-formed teeth.

The patient made an uneventful recovery.

The cyst had probably been present for about a year and a half prior to its recognition. Partial torsion must have occurred with the onset of the first severe attack of pain. The pedicle did not remain twisted, nor did the true cause of pain become manifest until the mass enlarged, due to hemorrhage occurring in the cyst when the venous return was cut off and the arteries were still pumping blood.

### Discussion

These two cases of ovarian cyst with torsion of pedicle were reported because of their rarity and the interesting points in their diagnosis. The diagnosis was obscure in the beginning, being confused with intussusception, acute appendicitis, and pyelitis. Neither case presented what are commonly considered characteristic symptoms, frequency and urgency. The presence of a pelvic mass palpated rectally should be almost conclusive evidence of a cyst. The condition in children would be recognized more frequently prior to operation if the possibility of torsion of an ovarian cyst were considered. The treatment is always surgical. The prognosis is good in children if operation is performed before peritonitis sets in.

### Summary

In summary, two cases of torsion of an ovarian cyst, one acute, the other chronic, are reported. One was an acute torsion of a simple cyst on the right side in a four-year-old child, while the other was a subacute, or chronic, torsion of a dermoid cyst on the left side in a twelve-year-old child. Both were accompanied by torsion of the tube and hemorrhage into the cyst. Frequency and dysuria were not a factor in either case. Symptoms followed defecation in one case, while no known precipitating factor was found in the other. The pain occurred

in paroxysms in both. There was no rigidity or temperature, and the patients were not acutely ill, even though operation was delayed in both cases. A pelvic mass was palpated rectally in one patient, abdominally in the other.

### Conclusion

Twisted ovarian cysts should be considered in any differential diagnosis of lower abdominal pain in female children.

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26 NORTH COLLEGE AVENUE

## PELVIC ACTINOMYCOSIS TREATED BY SURGERY AND ROENTGEN RAY, WITH RECOVERY

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**A**CTINOMYCOTIC infection of the internal genitalia of the female is uncommon and recovery is rare. Eighty-five cases of actinomycosis of the female pelvic organs have thus far been reported, of whom only 7 have survived. We wish to report an additional case apparently cured of this malignant disease.

Cornell in 1934 published a comprehensive survey of previously reported cases, of which there were seventy-one, to which he added one of his own. Thirteen cases have since been reported, four by Cote and Tudhope, two by Counseller and Horner and one each by Rumpf, Gardiner and Welsh, Morris, Joseph and Sommeral, Masson, Schockert and de Cooman, Junghans and Hüsey, bringing the total to eighty-five.

Gardiner and Welsh reported that only four cases had apparently recovered, namely, those of Horalek, Müller, Martius, and Sehngt, all of whom had been treated by surgery and x-ray. A patient of Cornell's, who was operated upon and later treated with potassium iodide, was well four years after operation. Masson reported a case apparently cured by operation and x-ray. A patient of Sanford's was in good health three years after treatment with potassium iodide, roentgen ray and radium. Of the seven cured cases, therefore, five were treated by surgery and x-ray, one by surgery and potassium iodide, and one by surgery, potassium iodide, x-ray and radium.

### Case Report

Mrs. E. P., a white woman 30 years of age, was admitted to the New York City Hospital on May 25, 1934. She complained of pain in the right lower abdomen, sacral backache, chills, fever, and retention of urine. Her past history included an attack of diphtheria in 1927, and extraction of carious teeth in September, 1933. Menstruation was normal. She had had two normal deliveries, the last in 1931.

Her present illness began in January, 1934, with an attack of sharp pain in the lower abdomen, followed by chills and fever, lasting a week. These symptoms subsided, but three similar attacks followed, during the four months before admission to the hospital. With the last attack she began to have difficulty in urination.

Physical examination revealed an emaciated, anemic, feverish young woman. Teeth and gums were in poor condition. The abdomen was tense, distended, and extremely tender over its lower half. There was moderate rebound tenderness and slight rigidity in the right lower quadrant. A mass could be outlined in the lower abdomen, extending almost to the umbilicus. The cervix was displaced forward against the symphysis by a bulging mass in the cul-de-sac. The uterus was not separately made out.

The temperature curve was of the septic type. The leucocyte count was 16,900, with 82 per cent polymorphonuclear leucocytes. There was a moderate secondary anemia, and a rapid sedimentation rate. Urine showed a trace of albumin and a few casts. X-ray of the chest and blood Wassermann were negative.

A preliminary diagnosis was made of acute exacerbation of chronic pelvic inflammatory disease, with pelvic abscess.

On May 28, the pelvic abscess was drained by posterior colpotomy. A quart of foul-smelling, greenish pus was obtained. The laboratory examination did not show sulfur granules or actinomyces. Following the colpotomy, the patient's condition improved only temporarily. During the next seven months, three more colpotomies were performed, pus being evacuated each time. In spite of these repeated drainages of the cul-de-sac, the patient continued to be seriously ill, with a high septic temperature, rapid sedimentation rate, hyperleucocytosis, and severe secondary anemia. Repeated blood transfusions were given.



Fig. 1.—Lobulated masses of mycelium in the liquid pus of an actinomycotic abscess.

When the temperature had remained normal for a month, although the sedimentation rate was still rapid, laparotomy was performed on December 10, 1934. There was a dense network of easily separated adhesions in the pelvis, with tubes, ovaries and uterus agglutinated to the cecum, sigmoid, rectum and anterior abdominal wall. The process grossly resembled that seen in cases of acute gonorrheal adnexitis following repeated recurrences. The tubes were dilated, thick-walled, tortuous, and contained thick pus. A bilateral salpingo-oophorectomy and supracervical hysterectomy was done. The pelvis was then drained through the posterior colpotomy wound and through the lower angle of the abdominal incision.

*Pathology.*—The pathology of this case was reviewed in detail by Lisa and Levine in the *Archives of Pathology*, January, 1937, and will be given here but briefly.

*Gross Findings.*—The specimen consisted of a uterus with an adnexal mass, and a separate tuboovarian tumor. The supracervically ampu-

tated uterus was grossly and histologically normal. The distal half of the attached tube was incorporated in a mass  $4\frac{1}{2}$  cm. in diameter, covered by a thick grayish-yellow exudate. On section, the tube and ovary could not be differentiated with certainty. The proximal half of the tube was free and very broad. It was covered with a thick granular serosa. On section, the wall was dense and firm. The lumen was dilated by a light-gray gelatinous material, surrounded by a narrow yellow zone. The separate tuboovarian mass was much larger, measuring 7 by 5 by 4 cm. It was similar to the attached mass, except that no free tube was present.

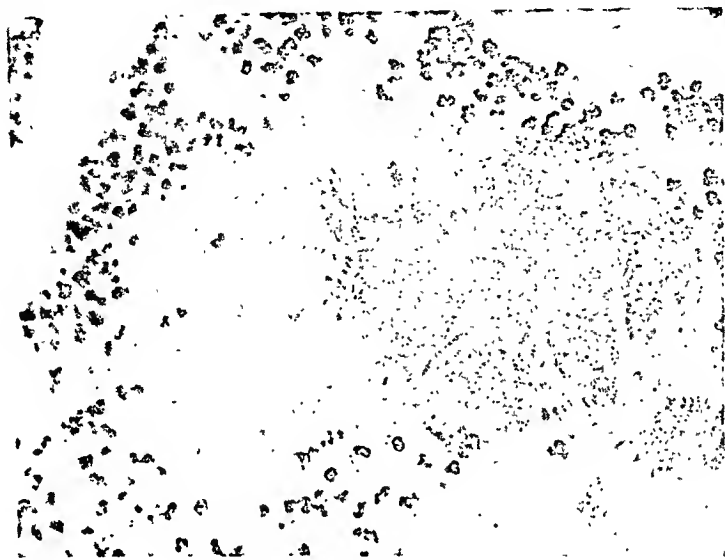


Fig. 2.—Filamentous structure of the central tangle of a knot of mycelium.

*Microscopic Findings.*—The adnexal tumors consisted of multiple actinomycotic abscesses containing lobulated masses of mycelium in liquid pus (see Fig. 1). The borders of the mycelium knots showed distinct radiation. Formation of typical clubs could be observed. On higher magnification the central tangles of the knots revealed a typical filamentous structure (Fig. 2). The immediate vicinity of the abscesses was converted into granulation tissue with some scar formation, indicating the chronic character of the actinomycotic granuloma (see Fig. 3). The granulation tissue consisted chiefly of mononuclear cells. The borders of the abscesses were necrotic, with abundant leucocytic infiltration.

A moderately severe wound infection developed four days after operation. Cultures showed streptococci and various bacilli. The infection responded to the use of Dakin's solution and the ultraviolet ray. In addition to blood transfusions and iron ammonium citrate, maximal doses of potassium iodide were administered. The patient was discharged much improved on January 15, 1935. At this time she weighed 102 pounds. Her weight had been as low as 72 pounds while in the hospital.

Several weeks later she appeared at the follow-up clinic with a tender, indurated mass measuring 7 to 8 cm., in the left lower quadrant of the abdomen. After another three weeks the mass had increased to

10 cm. in diameter, and a second mass had appeared on the right side, hard, fixed, and adherent to the anterior abdominal wall. Since potassium iodide had been ineffective in prevention of recurrence, its use was discontinued, and the patient was referred to the x-ray department of the Woman's Hospital, for x-ray therapy.

*Röntgen Ray Treatment.*—Treatment was begun tentatively, as there was not (and is not now) any established dosage procedure for abdominal actinomycosis. The tender, indurated mass in the left lower quadrant, measuring about 10 cm. in diameter, was first attacked. It was treated daily, starting February 25, 1935, through alternate anterior and posterior portals, at the rate of 300 roentgens per day.



Fig. 3.—Tissue of actinomycotic granuloma (scar formation).

Other factors were 200 kilovolts peak, 30 milliamperes, 70 cm. target-skin distance, 0.5 mm. to 1 mm. copper filter. Total roentgens in first cycle, 2,100 anterior, 2,100 posterior, given in a period of 3 weeks. The mass gradually diminished in size. A small residue was again treated in June, 1935, giving 100 r. daily to alternate anterior and posterior fields up to a total of 1,000 r. each. Two months later, in August, 1935, it had completely disappeared.

The right-sided mass, located at a higher level in the abdomen than the left and firmly attached to the anterior abdominal wall, was more recalcitrant. Treatment on it was commenced March 20, 1935, and continued at intervals until September 18, 1935. The first cycle, given more slowly than the first cycle on the opposite side, accumulated a total of 2,400 r. to each of the two portals used, over a period of seven weeks, ending May 9, 1935. On May 24, the mass seemed larger, and as the skin was in good condition, another cycle, totaling 1,800 r. anterior and 1,800 r. posterior was given. The mass shrank, but did not disappear, and from August 30 to September 18, 1935, a third and last cycle totaling 1,500 r. anterior and 1,500 r. posterior was given. Skin reactions were never excessive. The skin was in good condition at the end of the treatment, and remained so. By the end of November, 1935, there was no evidence of disease, and it has not recurred to date.

The patient received over her left-sided lesion totals within four months, of 3,100 r. (in air) to each of two opposing fields, anterior and posterior. The right-sided lesion, over a period of six months, received 5,700 r. per field, 11,400 r. altogether. The latter is among the highest doses reported in the cure of abdominal actinomycosis. The patient showed little evidence of satisfactory regression before the last cycle was given, so it seems unlikely that she was overtreated.

*Follow-Up.*—The patient was examined in March, 1940. She felt very well. There were no abdominal symptoms. Her bowels moved regularly. There was no pain, vaginal discharge or urinary symptoms. The cervix was freely movable, the parametria shortened, but contained no masses. Her weight was 149 pounds, a gain of 77 pounds since her lowest point in 1934.

She was seen again on February 17, 1944. She had no complaints. Her bowels moved regularly. The abdominal panniculus is moderate. There is a well-healed lower left paramedian cicatrix, with an umbilicated retraction at the lower angle, and a left lateral transverse scar about the middle of the incision, extending out for a distance of 1½ inches. Pelvic examination reveals the stump of a freely movable cervix. No adnexal or parametrial masses can be felt. Her weight is 148 pounds. There is a gain of 76 pounds since her lowest point in 1934.

Although first seen ten years previously, the purpose of this belated report is to note the complete recovery of the patient after this lapse of time.

### Summary

The clinical picture presented by our patient before operation was one of protracted, severe pelvic suppuration, with septic temperature, severe secondary anemia, and emaciation. Posterior colpotomy was performed on four occasions for the drainage of pus collections in the pelvis, with only temporary benefit.

Laparotomy was performed six and a half months after admission to the hospital, although the blood sedimentation rate was still very rapid. At operation, the findings resembled those commonly seen in cases of recurrent pelvic suppuration with tuboovarian abscesses.

In spite of hysterectomy and bilateral salpingo-oophorectomy, followed by large doses of potassium iodide, there was prompt recurrence in the abdomen. Roentgen ray treatment resulted in disappearance of the recurrences. The method employed, namely, surgery followed by fractional x-ray treatment with high total dosage, is probably the most effective in the treatment of abdominal actinomycosis.

Follow-up examination, five and ten years later, disclosed that the patient was well and there was no evidence of abdominal or pelvic disease.

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UNIVERSITY OF WASHINGTON  
SCHOOL OF NURSING  
REVIEW DIVISION

Special Article

OPHTHALMIA NEONATORUM\*

With Special Reference to the Sulfonamides in Treatment and the Continued Importance of Silver Preparations in Prevention

CONRAD BERENS, M.D., NEW YORK, N. Y.

IN THE school year 1906 to 1907, 28.2 per cent of the pupils admitted to schools and classes for the blind were blind because of ophthalmia neonatorum. In the school year 1941 to 1942, the percentage was 5.6.† These figures emphasize the great importance of the use of silver nitrate in the prevention of ophthalmia neonatorum and the value of the campaign waged by the National Society for the Prevention of Blindness for the use of this preventive measure.

The present communication is concerned chiefly with the newer methods of treatment, especially the use of the sulfonamides.

Recent studies seem to indicate<sup>1,2</sup> that silver is still the best preventive measure. However, silver nitrate also has its limitations in prevention. This has been demonstrated by Lehrfeld's<sup>3</sup> study of approximately 28,000 hospital birth records and 2,000 cases of ophthalmia neonatorum.

That silver acetate should be given consideration instead of silver nitrate is suggested by the studies of Rambo.<sup>4</sup> He found that in Hungary, a one per cent solution of silver acetate is used as a prophylactic for ophthalmia neonatorum. The advantage of this salt over silver nitrate is its safety. A one per cent solution of either salt is equally effective in preventing gonorrheal ophthalmia. The solubility of silver nitrate is very high, one gram being soluble in 0.4 gram of water. The solubility of silver acetate solution is one gram to 100 c.c. of water. Because of the low solubility of silver acetate, a stronger solution than is needed for infants' eyes cannot be prepared with water at room temperature. Rambo believes that "silver acetate has other properties, however, which would appear to make it more suitable to the needs of practice than the nitrate. While the latter is readily soluble in water, its solutions may gradually become concentrated by evaporation. Silver acetate crystallizes out as soon as a concentration of 1.2:100 is reached. Thus the danger of using too concentrated a solution is entirely precluded in the case of silver acetate."

\*Aided by a grant from the Ophthalmological Foundation, Inc.

†Percentage of blind children in the United States.

That silver proteins should not be used as substitutes is proved by the work of Muir<sup>5</sup> and Menshutin.<sup>2</sup>

The use of sulfonamides in the treatment of ophthalmia neonatorum has been discussed recently by numerous observers. Among these are Jensen<sup>6</sup> in 1939, Herman<sup>7</sup> in 1940, Schreiner,<sup>8</sup> Blanton<sup>9</sup> and Kadlicky<sup>10</sup> in 1941, and Demieheri, Chiazzaro and Uriarte<sup>11</sup> in 1942.

Gonorrheal ophthalmoblenorrhea has been successfully combated with sulfapyridine by Thrane.<sup>12</sup> Sourdille<sup>13</sup> reported a case of gonococccie ophthalmia successfully treated with di-(p-acetylaminophenyl)-sulfone. McKee<sup>14</sup> described the case of a man with the typical appearance of severe gonorrheal ophthalmia. Fifteen grains of sulfanilamide with 5 grains of sodium bicarbonate every six hours internally as well as the usual local treatment were administered. The discharge was noticeably less on the third day and had almost disappeared by the fifth day.

Blumberg and Gleich<sup>15</sup> believe that the sulfonamides used in the treatment of gonococccie ophthalmia neonatorum have greatly decreased the duration of the disease and have practically eliminated complications. Patients in their hospital are now treated routinely only with the oral administration of sulfathiazole. Local therapy and mechanical protection of the unaffected eye are apparently unnecessary. Sulfathiazole in doses of 1 grain per pound of body weight cured their patients and prevented complications.

The successful administration of the sulfonamides in the treatment of gonococccie conjunctivitis has been reported by Lewis<sup>16</sup> in 120 patients. Toxic reactions, with the exception of one case, early in the series, were practically negligible. Nausea occurred frequently, especially with the administration of sulfapyridine. Slight cyanosis was rather common. In very few cases were there any significant changes in the blood cell counts or in the hemoglobin. According to Lewis, there seems to be no contraindication to the systemic use of the sulfonamides except a definite history of previous intolerance to the drugs. He found the following: "Sulfapyridine is amazingly effective in the treatment of gonococccie infections of the eye. Sulfathiazole is apparently somewhat less effective. Both are definitely superior to sulfanilamide. A cure may be expected within three days, as a rule, from the time sulfapyridine treatment is begun." Recently, Lewis tried a 5 per cent solution of sodium sulfathiazole, instilled locally every two hours, combined with the usual dose of sulfathiazole internally. Apparently it is of definite value. He believes every patient with gonococccie conjunctivitis should immediately be given adequate systemic treatment with sulfapyridine or sulfathiazole.

According to Barbour and Towsley<sup>17</sup> sulfanilamide is a definite advance in the therapy of ophthalmia neonatorum for the following reasons: (1) The incidence of corneal complications has been diminished.

(2) Hospitalization has been reduced to an average of eight days with a minimum of complications but newborn infants tolerate and require larger quantities of the drug than adults to raise the blood concentration to the expected level.

In Muir's opinion<sup>4</sup> while sulfanilamide has produced more brilliant results than any previous therapeutic measure in the treatment of gonorrheal ophthalmia, it must be used with caution and a full understanding of its potential dangers. Muir believes that there will continue to be cases of gonorrheal conjunctivitis resistant to sulfanilamide, for which recourse to all available therapeutic resources will be necessary to prevent loss of the eye.

For the sulfonamide-resistant group, penicillin seems to offer great hope in general gonorrheal infections resistant to the sulfonamides. From several cases which have come to my attention, the same condition seems to be true concerning the local or general use of penicillin in eye infections caused by the gonococcus. If neither the sulfonamides nor penicillin prove effective, artificial fever therapy should be considered.<sup>5</sup> Mersurochrome<sup>18</sup> and other drugs have received consideration both in prophylaxis and treatment but greatest reliance should still be placed on silver nitrate and the sulfonamides (especially sulmyd [sulfacetimide]).<sup>19, 20</sup>

Once ophthalmia neonatorum has developed even the best treatment available often leaves many blind children, which are a burden either to the state or to the parents. It is important for physicians, especially obstetricians and ophthalmologists, to give serious consideration not only to the treatment but also to the prevention of ophthalmia neonatorum.

Safeguards for the prevention and treatment of ophthalmia neonatorum must be set up, that is: (1) Prenatal prevention—diagnosis and treatment of infections in the prospective mother; (2) Postnatal prevention—the use of a prophylactic in the eyes of the newborn infant and (3) universal use of the most modern and effective methods of treatment.

Because our knowledge of improved treatment of ophthalmia neonatorum apparently has lessened the hazards of this disease, it does not mean that preventive measures and prophylactic procedures should be discarded. Prevention is always preferable to cure regardless of the success of the treatment. In addition newborn infants are frequently attended by midwives or physicians at home deliveries in isolated communities and it could not be assumed that the necessary treatment facilities would be readily available.

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35 EAST SEVENTIETH STREET

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Endocrinology: Gynecology and Obstetrics

**Female Endocrinology Including Sections on the Male** is a sincere and earnest attempt to present the rapidly accumulating evidence covering this interesting field. The author has worked for many years, both in the laboratory and in the clinic, which, together with his wide knowledge of the literature, enables him to give a full presentation.

The volume is divided into three sections—physiology, clinic and laboratory. Of this, physiology covers 286 pages, which include development, the function of the ovary from every aspect. The safe period, the endocrine factors in menstruation and uterine motility are discussed. The endocrine role of the placenta, the physiology of parturition are taken up as well as that of the breasts. A chapter is devoted to the physiology of the testis. After this, the function of all individual endocrine glands is dealt with, with particular regard to any connection with the genital sphere. These chapters are very satisfactory, being complete, yet short and incisive and complimented, as is carried out through the book, by a satisfactory bibliography.

The clinical portion covers particularly the functional diseases, including deficiencies and excesses of menstruation. Here the innumerable etiological causes assigned by various authors are discussed in the light of the large experience of the writer. It is not surprising that in this very debatable field the reviewer is unable to agree with many of the interpretations. However, in the main, the therapeutic measures recommended are conservative and justifiable. The same applies to even a greater degree to the chapter on dysmenorrhea and spontaneous and habitual abortion. In the latter, the Rh factor has not as yet been incorporated. A chapter on abnormal manifestations arising during gestation, covers toxemias, endocrine aspects of dystocias and maternal tetany. Abnormalities of the breast are taken up. An excellent chapter on obesity follows. Preceding the discussion of the long list of endocrinopathies, is a chapter on constitutional types. The clinical portion of the book ends up with the discussion of cryptorchidism, sex determination and differentiation, and hermaphroditism.

The concluding portion of the volume deals with the laboratory. This part of the subject is handled briefly, in detail and yet within short compass. It includes the usual aids, endometrial biopsy and vaginal smears, sex hormone tests with description of the techniques, the hormonal findings in blood and urine, and concludes with a detailed description of the hormonal preparations available, their indication and dosage.

An authors' index is valuable in making the access to the huge bibliography easy. The illustrations, many of which are from different sources, are excellent. The entire book is satisfactory, well written and interesting. In dealing with a subject which is in such a fluid state as our present knowledge of endocrinology, it is not indicated to take exceptions to different view points which may or may not stand the test of time.

R. T. FRANK.

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<sup>1</sup>**Female Endocrinology Including Sections on the Male.** By Jacob Hoffman, A.B., M.D., Demonstrator in Gynecology, Jefferson Hospital; Formerly Research Fellow in Endocrinology and Director of the Endocrine Clinic, Gynecological Department, Jefferson Hospital, Philadelphia. Fully illustrated including some in colors. 788 pages. W. B. Saunders Company, Philadelphia, 1944.

**Human Constitution in Clinical Medicine** by Draper, Dupertuis and Caughey<sup>2</sup> is of interest and instructive value not only for the medical student for whom it is primarily designed, but also for every medical man, particularly for specialists who are too apt to concentrate upon one organ at the expense of the individual, not only in medicine, but also to pick the right man for the right job. To surmise what diseases an individual will be most likely to develop, constitutional factors, anthropometric measurements, photographic somatotyping, and overall correlation of features is essential. These studies deal with the essence of personal identity. The authors are well aware that some of their techniques, for instance the short cuts to the psyche, leave much to be desired, but even with these shortcomings, one should be able to predict the response of a given individual to the pressure of the whole environment, based on his personality. The foundations for this monograph were developed in the Constitutional Clinic of the Presbyterian Hospital of New York City, with aid of the Rockefeller Foundation and the Markle Foundation.

By means of methods described, one should be able to gauge the strength, the weaknesses and the qualities of a given patient, and to evaluate how much the patient himself contributes to his own disabilities. Psychiatrists have focused more upon the personal identity of the individual than any of the other disciplines in medicine. The methods for explaining the nature of Man are manifold. The response to external stimuli, be they bacterial, worry or overstrain, are different in each person. To obtain data, the authors outline the methods of history taking, with special regard to personal inheritance and personal diseases. They illustrate these methods by few but well-chosen and striking clinical examples. The same applies to every one of the methods they utilize. Among the subjects taken up are genetics as applied to clinical medicine, particularly inheritance factors and vulnerabilities. Another chapter takes up growth, development, decline and death. Under androgyny, they discuss especially nongenital attributes of sex and their variation. Anthropometry, somatotypes and especially constitutional physiology are discussed.

This stimulating volume does not attempt to do more than lay the foundation for accurate observation of factors too often neglected by the clinician, and yet of utmost value in sizing up individuals, their strength and weaknesses, and how these affect the wear and tear which life entails. The book is to be highly recommended because it should stimulate further and more detailed study along these lines.

R. T. FRANK.

The second edition of Greenblatt's **Office Endocrinology**<sup>3</sup> appears after three years. It covers a much wider field than the first edition. In fact, on looking over the index, a tremendous amount of subjects have been dealt with. It is the kind of book that contains a treatment for every ailment discussed. Apparently the most popular endocrine remedy is testosterone in one form or another. However, I am afraid a great many readers, when applying the recommended therapy, will meet with disillusion. For example, the first in the list of treatments for female sterility is, "Gentle dilatation of the cervix is frequently followed by conception. Action: a. Indirect stimulation of the ovaries. b. Promotion of cervical drainage."

R. T. FRANK.

<sup>2</sup>**Human Constitution in Clinical Medicine.** By George Draper, M.D., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, Presbyterian Hospital, New York City; C. W. Dupertuis, Ph.D., Physical Anthropologist, Constitution Clinic, Presbyterian Hospital, New York City; and J. L. Caughey, Jr., M.D., Med. Sci. D., Associate in Medicine, College of Physicians and Surgeons, Columbia University. Assistant Physician, Presbyterian Hospital, New York City. 273 pages. Paul B. Hoeber, Inc., Medical Department of Harper & Brothers, New York. 1941.

<sup>3</sup>**Office Endocrinology.** By Robert B. Greenblatt, B.A., M.D., C.M., Professor of Experimental Medicine, University of Georgia School of Medicine; Director, Sex Endocrine Clinic, University Hospital, Augusta, Georgia. With a foreword by G. Lombard Kelly, M.D., Dean, University of Georgia School of Medicine. Second Edition. 243 pages. Charles C Thomas, Springfield, Illinois. 1944.

1943 Year Book of Obstetrics and Gynecology edited by By Dr. Greenhill<sup>4</sup> brings 565 pages of abstracts of important articles, well selected and concisely presented, in the annual literature of the two subjects. One finds here practically all of the new refinements in operations and treatments as well as the recent advances in research and clinical practice. Greenhill has devoted some fifteen pages to caudal anesthesia, and concludes with the statement that he does not believe the method will become a part of our general obstetric armamentarium. He repeats the advantages of local anesthesia for various obstetric maneuvers. There is considerable discussion of the Rh factor and the recent literature on endocrines and sulfonamides.

The book is unexcelled as a quick reference to the literature.

PHILIP F. WILLIAMS.

The report of the first Brazilian Congress of Gynecology and Obstetrics appears in three volumes<sup>5</sup> totaling over 1,500 pages. This Congress was held at Rio de Janeiro in September of 1940, under the presidency of Professor Arnaldo de Moraes. The Congress took up four main themes—recent advances in gynecological hormonology; the diagnosis and therapy of cervical cancer; endocrine diseases in pregnancy; and obstetrical care which includes the preconceptional, prenatal care, maternal mortality, neonatal mortality, and the social aspects and agencies.

The attendance appeared to be mainly local although some Argentine and Chilean physicians attended.

The recent advances in gynecological hormonology was introduced by a very detailed consideration of the steroid and gonadotropic hormones by Doctors Alameda and Salaber. This likewise covered the physiology and application of these substances. The experimental and clinical aspects were treated by Salgado and Monteiro de Barros, dealing with the use of the male hormones in gynecology. A short paper by Slotka, who is now in São Paulo, dealt with the chemical aspects of the steroid.

Among the many papers on cervical carcinoma is that of Wood, Cruz and Galán. They place a great deal of value on the Schiller test and state that the earliest diagnosis of what I take to be suspected lesions, results in 100 per cent cure by mere amputation of the cervix. On the whole, they favor radiotherapy (x-ray and radium) except in radioresistant types, in which radiation is followed by radical operation.

Among endocrine diseases in pregnancy, diseases of the thyroid and parathyroid, of the adrenals, hypophysis and diabetes are taken up. In addition to the main themes, a large number of mainly casuistic reports are included. The volumes are gotten up faultlessly, are profusely illustrated, and contain the discussion. From these reports, it is evident that not only is the available material very abundant, but also that pathology, experimental investigations and therapy are on a very high level.

R. T. FRANK.

Histerosalpingografía by Buteler<sup>6</sup> represents a bulky doctoral thesis. The work was done under the auspices of the University of Cordoba in Argentina. It is based on 450 cases. The monograph is illustrated profusely and adequately. The author uses iodized oil of local manufacture. He emphasizes that fluoroscopy and manometric control are essential. In special instances, pneumoperitoneum may be in-

<sup>4</sup>The 1943 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago. Pages 565. The Year Book Publishers, Chicago. 1944.

<sup>5</sup>Anais Do Primeiro Congresso Brasileiro De Ginecologia E Obstetricia. Professor Arnaldo de Moraes, President. Vol. I, 548 pages. Vol. II, 450 pages. Vol. III, 508 pages. Jornal Do Commercio, Rodrigues & C., Rio de Janeiro. 1942.

<sup>6</sup>Histerosalpingografia. By Eduardo Buteler. 381 pages. Universidad Cordoba, República Argentina. 1943.



duced at the same time. He obtains much better pictures while the cervix is occluded. No mention of aqueous media for salpingography is made. There are many misprints of dates, as, for example, the beginning sentence in which Dartigues is supposed to have used roentgen rays in 1867.

R. T. FRANK.

The collaborators and pupils of Professor Josué A. Beruti<sup>7</sup> have collected and republished all of his many contributions to the medical literature in four large volumes, totaling 2,241 pages. Acknowledgment is made to many of the pharmaceutical houses who probably have contributed. This publication commemorates the twenty-fifth anniversary of professorship at the Medical School of the University of Buenos Aires. Professor Beruti started his medical publications in the year 1902 and the collection extends to 1943 inclusive. The entire sphere of obstetrics is included, covering physiology of pregnancy, of the puerperium, pathologic deviations, operations and many subjects which embrace such diverse topics as female education, scientific propaganda and cultural diplomacy of Germany in Argentine and even funeral orations. These volumes cover the actual activities of a man of wide interests.

R. T. FRANK.

Dr. Raúl García Valenzuela has published a monograph on the **Treatment of Septic Abortions** which he utilized as the thesis for obtaining the title of clinical professor at the University of Chile. The thesis is based on 300 cases of which 52 per cent were definitely determined as of criminal origin. This covers a period of two and one-half years. There were 15 serious complications, including 3 embolic ones.

The treatment appears to consist of observation for a few days, the giving of drugs helping to contract the uterus in order to aid emptying of the cavity. Where there is persistent retention, a cautious emptying of the uterus is performed. The sulfa drugs have been used. A full discussion, particularly of the Latin American literature as well as the German sources, is given. It is noticeable that in 1,716 cases extending from 1934 to 1942, the overhead mortality has decreased from 27.9 per cent to 8.8 per cent. The monograph concludes with short case histories of 300 patients. There is nothing particularly new in the presentation.

R. T. FRANK.

The sixteenth edition of **Care and Feeding of Children** by L. Emmett Holt,<sup>9</sup> appears on its fiftieth anniversary. The long continued use of this book is a memorial to its value. In these days of juvenile delinquency and wartime hysteria among adolescents, one feels that a reading, by many parents, of the chapter on "Behavior Problems," would do much toward understanding and curbing some of our present social difficulties. A chapter "How to Prevent Accidents" should be ready by all who have small children. It contains sound advice.

The present edition of this book should continue to be as popular as its predecessors.

PHILIP F. WILLIAMS.

<sup>7</sup>Producción Científica y Cultural de Josué A. Beruti. Obstetricia Ginecologia, Medicina Social, Cuestiones educacionales, universitarias, hospitalarias, etc. Homenaje de Sus Colaboradores y Discipulos de la Catedra de Clinica Obstetrica y de Sus Amigos. Tomo I, 472 pages; Tomo II, 628 pages; Tomo III, 601 pages; Tomo IV, 539 pages. Alfredo Frascoll, Buenos Aires. 1943.

<sup>8</sup>El Problema Terapéutico Del Aborto Séptico. By Raúl García Valenzuela, Profesor de la Escuela de Obstetricia y Puericultura de la Universidad de Chile. 156 pages. Universitaria, Santiago de Chile. 1943.

<sup>9</sup>Care and Feeding of Children. By L. Emmett Holt, M.D. Revised and enlarged by L. Emmett Holt, Jr., M.D., Associate Professor of Pediatrics, Johns Hopkins University. Pages 314. D. Appleton-Century Company, New York and London. 1943.

Doctor Castallo and Andrey Walz have presented in *Expectantly Yours*<sup>10</sup> a pleasantly and, often, amusingly told story of maternal care.

Many obstetricians will endorse the comments on the effect of illegal abortions on mortality statistics. The "Facts of Life" are just as scientific as in any average book of the same nature but the redressing of them by the junior author makes them more easily read and understood. Little of importance has been omitted in the discussion of prenatal hygiene and labor. The comparison of various methods of analgesia should amply supply the average woman's curiosity in this matter.

The chapter entitled, "The Come Back," is excellently done, it is a good story of the puerperal state, and Doctor Castallo's wise note on birth control is well placed. For the patient who wants or needs, according to her temperament, a manual in a lighter vein with an occasional smile, and yet, with plenty of solid information, this book fills the need.

PHILIP F. WILLIAMS.

Dr. Carrington offers in *Safe Convoy*<sup>11</sup> a very comprehensive textbook for the expectant mother. He has divided the material into nineteen chapters covering all phases of pregnancy, labor, puerperium and infant care. There are few questions which the pregnant woman may ask her physician that are not specifically answered in this book. Dr. Carrington states in his preface of the book that it is not intended to replace ante-partum care with the physician, but to enable the woman to understand fundamentals so that she may cooperate more intelligently with her doctor. In these busy days of obstetric practice, this book should be a boon to women unable to contact their obstetrician easily.

One likes, particularly, Dr. Carrington's discussion on analgesia and anesthesia and is in accord with his feeling that very little of these methods are necessary in the average birth. The style of presentation is delightful for Dr. Carrington illustrates almost every section with allusions to comparable situations in biblical, historical and even recent popular literature. The final chapter of the book on "Fathercraft" is an excellent inclusion. Few obstetricians ever have the chance to talk to prospective fathers. This chapter tells him what his wife's physician would like to say to him early in the pregnancy so the book may be well recommended to both father and mother of the baby to come.

PHILIP F. WILLIAMS.

The *History of Gynaecology*<sup>12</sup> is determined primarily by two factors, by the position of woman in society, and by the status of medicine, which itself is largely the result of the social and economic conditions of a given period and of its technology. Indeed, the more the physician knew about the anatomy, physiology and psychology of women, and about the causes and pathogenesis of disease, the more effectively he was able to help. On the other hand, it made a great difference whether woman was considered a beast of burden, the "door to hell" (*janua diaboli*), or whether she was worshipped. A history of gynecology is therefore by necessity, a combination of social and medical history.

<sup>10</sup>*Expectantly Yours*. A book for Expectant Mothers and Prospective Fathers. By Mario A. Castallo, A.B., M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Medical College, and Audrey Walz. Pages 110. Illustrations 14. The Macmillan Company, New York. 1943.

<sup>11</sup>*Safe Convoy*. The Expectant Mother's Handbook, by William J. Carrington, A.B., M.D., F.A.C.S., Attending Gynecologist, Atlantic City Hospital. Pages 253. J. P. Lippincott Company, Philadelphia and New York. 1944.

<sup>12</sup>*The Genealogy of Gynaecology*. History of the Development of Gynaecology Throughout the Ages, 2000 B.C.—1800 A.D., with Excerpts from the Many Authors Who Have Contributed to the Various Phases of the Subject. By James V. Ricci, A.B., M.D., Associate Clinical Professor of Gynaecology and Obstetrics, New York Medical College; Director of Gynecology of the City Hospital, New York, etc. Chapters xxi; 578 pages. Illustrated. The Blakiston Company, Philadelphia, 1943.

The present book unfortunately does not attempt to be such a history. It follows the traditional pattern and is basically a huge and heavy compilation of undigested and frequently misunderstood data. At the beginning of every chapter the author discusses the "historical background" of the period, but his picture is always conventional and he never attempts to correlate the background with his narrative. There is no doubt that the eighteenth century was filled with diplomatic intrigues, dynastic rivalries, and interminable wars, but for an understanding of the history of gynecology, it is more important to remember the great part played by women in that century, the rise of the middle class, or the beginning of the industrial revolution which was to influence the social position of woman and her entire pathology so considerably.

The author has undoubtedly devoted much time and labor to the preparation of his book. His bibliographies look very impressive, but unfortunately he worked a great deal from secondary sources and used good and bad books, modern scholarly studies and outdated uncritical monographs, without any discrimination. Hence, when he happens to follow a good source his statements are correct, but when the source is bad, he does not hesitate to tell the most fantastic stories. Thus he still believes that the early temples of Æsculapius were medical schools and mentions Epidaurus, Cos and Cnidus in one breath (p. 47). Being unaware of the archeological literature on Cos, he still thinks that there was a temple of Æsculapius on that island at the time of Hippocrates (p. 52), while the excavations of Herzog have demonstrated unmistakably that the cult of Æsculapius was not introduced before the middle of the fourth century B.C., that is, after Hippocrates' death, and that the temple was built in the beginning of the third century.

Speaking of Salerno, the author states that the Salernitan masters of the twelfth century "did not take kindly to Arabic influences" (p. 244). The contrary is true. He mentions among others Nicolaus Praepositus, but if he had known a study of Wickersheimer published in 1911, he would have found that Nicolaus Prepositi was a sixteenth century French physician,\* and if he had known a book that I wrote over twenty years ago,† he would have seen that the Salernitan Antidotarium Nicolai is conspicuous for its Arabic influence. It would be easy to point out dozens of similar mistakes due to mere ignorance of the basic literature.

Wrong dates are always disturbing, but particularly so when a date marks a turning point. The illustration of the female genitalia from Johannes de Ketham (p. 287) is not from the edition of 1491, and this is precisely why it is significant. The edition of 1491 had a totally different, purely diagrammatic, traditional illustration, while only two years later, the publisher felt that he could no longer present the public with such mediaeval pictures and had a new, realistic one drawn by a Renaissance artist, the picture that is found in the various editions from 1493 on.

One cannot help feeling that the author has not read all the sources he quotes. When he gives the title of a book in Greek characters, every accent is wrong (p. 205); when he quotes Latin texts and omits the verbs or other crucial words, so that the sentence does not make sense (pp. 251, 289); when he refers to Pseudo-Apuleius as Apuleius Barbatus, the bearded Apuleius, instead of Apuleius Barbarus, as he was sometimes wrongly called (p. 168), it certainly sounds strange.

It is highly regrettable that the author did not consult the best history of ancient gynecology that has ever been written, that of Paul Diepgen, a book that was published in 1937, and that can be found in every large medical library.‡ Diepgen

\*Ernest Wickersheimer, Nicolaus Prepositi, ein französischer Arzt ums Jahr 1500. *Archiv für Geschichte der Medizin*, 1911, Vol. V, pp. 302 ff.;—*Bulletin de la Société Française d'Histoire de la Médecine*, 1911, Vol. X, pp. 388-397.

†*Studien und Texte zur frühmittelalterlichen Rezeptliteratur*. Leipzig, Johann Ambrosius Barth, 1923 [Studien zur Geschichte der Medizin herausgegeben von der Puschmann-Stiftung an der Universität Leipzig, Heft 13].

‡Die Frauenheilkunde der alten Welt. In: *Handbuch der Gynäkologie*, herausgegeben von W. Stoeckel, 12. Band, 1. Teil, München, 1937, Verlag von J. F. Bergmann, 348 pp.

has practiced gynecology for many years, and is one of the most distinguished and most competent medical historians of our time; professor of the history of medicine and director of the Berlin Institute since 1930. His book is the result of thirty years of historical research, is based entirely on original sources and fully documented. If our author had taken the trouble to compare his findings with those of Diepgen and had looked up the sources quoted by Diepgen, he would have been spared an endless number of mistakes.

Another shortcoming that must be mentioned and for which the publisher is as much to blame as the author, is the fact that the book has literally hundreds of typographic errors. French words possess accents; this may be unpleasant, but the accents cannot be disregarded. German words are inflected and wrong endings may change the meaning of a sentence. The book looks as if it had been printed without any proofreading from an uncorrected manuscript.

It is very discouraging to see such books published at a time when great efforts are made to raise the standard of medical historiography, and when institutions are available where a student can seek expert help and advice. An amateur can make valuable contributions to the history of medicine, provided he is aware of his limitations and selects a subject that he is equipped to handle. A history of gynecology that covers 3,800 years of human civilization is the most ambitious task that a historian can set for himself. It requires not only gynecologic knowledge, but a complete mastery of the methods of historical research, and the writer of such a book must be equally at home in the fields of anthropology, Oriental philology, classics, mediaeval, Renaissance and modern studies.

It will take years of effort to eradicate the mistakes that this book is perpetuating.

HENRY E. SIGERIST.

### Miscellaneous

**Psychosomatic Medicine**,<sup>13</sup> written by an internist trained in psychological medicine, and a psychiatrist with wide experience in the field of general medicine, deals with the clinical application of psychopathology to general medical problems.

After a short but inclusive chapter devoted to personality development and psychopathology, the authors consider in systematic fashion the psychosomatic aspects of the disorders and diseases of the various bodily organs and systems. The glands of internal secretion and their relation to personality disturbances; the sexual function and its relation to general medicine; such common problems as headache, constipation and sleeplessness are dealt with from the standpoint of their emotional implications.

Perhaps the most valuable section of the book is that portion which deals with treatment. Here methods of eliciting a psychosomatic history, the presentation of the explanation of psychosomatic illness to the patient and the general principles of psychotherapy are discussed. A useful chapter discusses such common "normal" problems in psychotherapy as the feeding problems of infancy and childhood, sexuality of childhood, problems of adolescence, marital maladjustments and divorce, the psychology of pregnancy and parturition and the psychosomatic problems of aging. All of this material will be of interest to the obstetrician and gynecologist.

The last World War gave great impetus to the development of modern psychiatry. The publication of this timely book suggests that the present World War will provide the basis for a more final integration of psychiatry into general medicine, in other words, what is here spoken of as psychosomatic medicine.

PHILIP F. WILLIAMS.

<sup>13</sup>**Psychosomatic Medicine. The Clinical Application of Psychopathology to General Medical Problems.** By Edward Weiss, M.D., Professor of Clinical Medicine, Temple University Medical School, Philadelphia, and O. Spurgeon English, M.D., Professor of Psychiatry, Temple University Medical School, Philadelphia. Pages 659. W. B. Saunders Company, Philadelphia and London. 1943.

This comprehensive text, 766 pages, *The Hospital in Modern Society* by Bachmeyer and Hartman<sup>14</sup> is a collection of material from the literature for those interested in hospital administration. These articles have been carefully selected and adopted. Unfortunate delay in publication has prevented the inclusion of articles subsequent to 1940, although bibliographies for most chapters have been brought up to July, 1943.

The book is divided into five parts, taking up the origins and use of hospitals; organization and management of hospitals; the medical and nursing staffs as well as the special intramural services, financial, maintenance, administration, and public health aspects; and, finally, the relationship of hospital to community and public health. The various chapters in this part of the book are composed of adaptations of discussions of specific hospital problems as they have appeared in the literature and each section answers the question that may be brought up by the various personnel staffs of the institution.

The chapter on obstetric services contains articles by Dr. Bingham, Miss Konrad and Dr. Cornell. Although these articles are dated several years previously, they are just as effective today as when they were written. Other chapters of interest to medical services, at least, should be those regarding the operating room, x-ray, laboratory and other sections of the hospital with which the physician comes into daily contact.

The chapter on legal aspects should be read by all medical staff members. Not the least interesting parts of the book are the discussion of group hospital and health insurance, and the chapter on public health. It is to be regretted that these sections are not up to date, in view of the developments in these fields in the last few years. One regrets particularly, the section by Dr. Thomas Parran entitled, "Next Objectives," could not have been rewritten in recent months.

The volume is really a most important book for all hospital libraries, and for those both lay and professional, who wish to comprehend the underlying problems of hospital administration and management.

PHILIP F. WILLIAMS.

*Standard Nursing Procedures of the Department of Hospitals, City of New York*,<sup>15</sup> was prepared by a Committee of Nurses advised by numerous physicians. It may be considered a reference book, which should be of use to all who are instrumental in teaching nursing, as well to administrators of hospital nursing. A very interesting history of the development of the department of hospitals in New York City begins the volume. The first almshouse in New Amsterdam was opened in 1653. The first private hospital may be said to date from 1660 when the Dutch West India Company built it for its slaves, seamen and soldiers. In 1784, the close of the Revolution, the New York hospital system for the poor may be said to have originated.

A detailed guide for basic nursing care covers more than 300 pages. Special nursing procedures include obstetric nursing, nursing of infants and children, and the basic procedures in neurological nursing. This detailed guide concludes with a short chapter on the hospital in the community, written by Bernecker, the present Commissioner of the Department of Hospitals.

The text is arranged for rapid orientation and for obtaining detailed information readily. While the average nurse will find the contents too voluminous, it will prove of great assistance to supervisors and teachers.

R. T. FRANK.

<sup>14</sup>*The Hospital in Modern Society*. Edited by Arthur C. Bachmeyer, M.D., Director, University of Chicago Clinics, Director, Hospital Administration Course, University of Chicago, and Gerhard Hartman, Ph.D., Director, Newton Hospital, Newton Lower Falls, Mass. Pages 766. The Commonwealth Fund, New York. 1943.

<sup>15</sup>*Standard Nursing Procedures of the Department of Hospitals, City of New York*. Prepared by the Committee of Nursing Standards, Division of Nursing, Department of Hospitals, Mary Ellen Manley, R.N., M.A., Director. 436 pages. The Macmillan Company, New York. 1943.

The aim of this book, *Applied Dietetics* by Frances Stern,<sup>16</sup> is to present a procedure for planning and teaching normal and therapeutic diets. The book is divided into four parts which take up the construction of such diets, tables for computing diets, a series of dietary outlines for the treatment of various diseases, and an illustration of how food prescriptions may be filled.

There are two very important chapters in Part I—the education of the patient on a normal diet, which should give physicians and others concerned many ideas on lay education in nutrition. The following chapter continues the same ideas as applied to therapeutic diets. Such advice as given here should be very helpful.

There have been many advances in nutrition since the first edition in 1936, and one will note here most recent findings concerning the vitamins, mineral values of foods and vitamin deficiencies. It is stated that the section on diabetes has been completely revised.

As far as the obstetrician is concerned with nutrition, he will find here excellent material on the nutritional needs of pregnant women both in the normal state and where complications are present. There are sample diets for pregnant patients with chronic nephritis, pernicious vomiting, and for eleven other abnormal conditions which are frequently found associated with pregnancy. Since the majority of pregnant women are either overweight or underweight, the obstetrician may find some excellent material on the chapters on obesity and underweight. All these sample diets for pregnancy or complicating diseases are worked out in terms of menus as well as nutritional factors.

The book should be of interest and value to many groups of professional people who are interested not only in normal nutrition and in prescribing dietary therapy for various diseases and conditions.

PHILIP F. WILLIAMS.

The second edition of *Pioneers of Pediatrics* by Dr. Levinson,<sup>17</sup> within seven years, shows that this book actually has met a demand. The subject matter covers children's disease and children's care from the earliest time, beginning with Hippocrates, who described mumps, and covering the Islamic, the fifteenth to eighteenth centuries, then proceeding up to the present time. Some of the high marks are Jenner's introduction to vaccination; Heine, who in the nineteenth century described poliomyelitis; the work of Holmes, Semmelweis, Credé, Hutchinson, Barton, von Behring, Still, von Pirquet and Schick. The pioneers of infant feeding, those who investigated alimentary disturbances are mentioned, and finally the American pioneers of pediatrics. Only very few living physicians are included. There are numerous full-page portraits which add to the value of this brief abstract of history.

R. T. FRANK.

<sup>16</sup>*Applied Dietetics*. The Planning and Teaching of Normal and Therapeutic Diets. By Frances Stern, Chief of Frances Stern Food Clinic, The Boston Dispensary, Assistant in Medicine, Tufts College Medical School. Second Edition. Pages 225. Tables 57. The Williams & Wilkins Company, Baltimore. 1943.

<sup>17</sup>*Pioneers of Pediatrics*. By Abraham Levinson, B.S., M.D., Assistant Professor Pediatrics, Northwestern University Medical School; Professor of Pediatrics, Cook County Graduate School of Medicine; Attending Pediatrician, Children's Division of the Cook County Hospital; Senior Attending Pediatrician, Sarah Morris Hospital for Children of the Michael Reese Hospital; Senior Attending Pediatrician, Mount Sinai Hospital, Chicago. Second Edition; Foreword by I. A. Abt. 119 pages. Froben Press, New York. 1943.

## Correspondence

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### The Role of the Physician in Child Adoption

*To the Editor:*

Although proper procedures for child adoption are available, they differ unfortunately in various states. Moreover, such information is scattered either throughout numerous periodicals, or else is contained in special books with limited distribution and publicity. A sad incident in this connection, which undoubtedly occurs more frequently than is usually recognized, took place recently with which I, as the obstetrician handling the case, was personally involved. My experience in this instance is worthy of dissemination to others who may be confronted some day with a similar problem.

An unmarried, pregnant primipara was referred to me for obstetrical care. Owing to religious tenets, she was accordingly desirous of giving birth to the baby, but subsequently planned to place the child in the hands of adoptive parents. During the entire ante-partum period, through the power of suggestion, I tried to stimulate her to keep the child herself when it arrived so that it might receive the love and affection of its own mother. She remained determined in her wish "to give the child away" soon after its birth, even to the point of refusing to see the child when it would be born.

In due time, a normal male child was uneventfully delivered. While the patient was in the hospital following delivery, I again tried to impress upon her the advisability of bringing up the child herself but to no avail. She stubbornly refused even to see the child and insisted that it be given for adoption.

The problem of a suitable disposition of the child then arose. The expressed desire of the patient was that it be placed directly in the home of adoptive parents without the intervention of any religious, social or welfare agency. Although the advantages of adoption committees were explained to the mother, for some reason or other she did not entertain the idea for even a moment. She seemed to be of the belief that the particular social or religious agency in this State (New York), to which the child would be forwarded, might send her baby to a "home" or an orphanage. I could not change her mind and unfortunately allowed myself to consent to her wishes for "private adoption." One of my medical colleagues contacted me about obtaining this child for a member of his family whose marital life was barren and although I was reluctant to be a party to a private adoption, he could see no ill effects from it. Despite my warning that in this State the mother could always claim the child at any time prior to granting of the final and legal adoption papers by the Surrogate's Court (a six-month period of time must elapse during which investigations are made of the conditions in the home of the adopting parents before obtaining permanent and legal parenthood of an adopted child), the physician for the adoptive parents minimized such an occurrence. He explained that he had fully acquainted the prospective parents with the possibility of the mother changing her mind but that they were willing to chance the risk.

Accordingly, the mother willingly gave temporary custody of the child to the new parents through the necessary papers arranged by their attorney and the child was taken from the hospital and delivered to its newly-acquired parents. The ten-day-old infant was immediately accepted gratefully as a member of the household.

A trained baby nurse was placed in complete charge of the baby and the child prospered. The love and affection of the adoptive parents for the child steadily grew. Not only the "parents" but even the "grandparents" of the baby were completely enthralled by the baby, so much so that the manner of its accession had been quite forgotten.

All seemed well, but like the calm before the storm all was not well. At about this time, my patient appeared at the office (three months post partum) and with determined resolution stated that she wanted the child returned to her. She informed me that she was well within her legal rights and that during the past three months she had sufficient time for reflection. Her decision to claim the child was definite and any attempt of mine to now interfere was futile (since I had constantly urged this very thing during the months prior to confinement). I made her wishes known to the other physician. The adoptive parents contested the action in court but in the end, the child was returned to its true mother. It is needless to describe the extreme hurt which the adopting mother and father experienced.

It is not within the province of this correspondence to take issue with the decision of the court since the law of the state is clear and the verdict was technically justified. The real reason for telling of this experience is to acquaint the profession with the proper method of child adoption. If there exists in the respective state in which the physician resides an agency or adoption committee especially devised for this purpose, the doctor *should insist* upon such an agency handling the adoption of a baby. Such stories as I have related are not uncommon, they are far too frequent as close scrutiny of court records will disclose. Social agencies and specialized adoption committees that have studied the problem certainly are far better equipped to make decisions in this matter than physicians, who are ignorant of the possible consequences. In the final analysis, the physician is a highly trained technician whose education in welfare work has been neglected, while welfare agencies have improved to such an extent that the states of our Union have seen fit to grant them special privileges in the handling of children for adoption which obviates such cruel episodes as suffered by all involved in the case described above.

ABNER I. WEISMAN, M.D.

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# Society Transactions

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## NEW YORK OBSTETRICAL SOCIETY

*MEETING OF NOVEMBER 9, 1943*

The following paper was presented:

**Some Observations on the Use of Caudal Analgesia in Obstetrics.** Clifford B. Lull, M.D. (by invitation). (For original article, see page 312, March, 1944, issue.)

*MEETING OF DECEMBER 14, 1943*

The following papers were presented:

**Transplantation of Abdominal Fascia for the Relief of Urinary Stress Incontinence.** William E. Studdiford, M.D. (For original article, see page 764.)

**Endometriosis Interstitiale With a Report of Three Cases.** James R. Miller, M.D., and Robert Tennant, M.D. (For original article, see page 784.)

*MEETING OF JANUARY 11, 1944*

The following papers were presented:

**A Previlious Human Ovum Accidentally Recovered in a Curettage Specimen.** Andrew A. Marchetti, M.D.

**The Elderly Primipara.** Katherine Kuder, M.D. (by invitation), and Donald G. Johnson, M.D. (by invitation). (For original article, see page 794.)

*MEETING OF FEBRUARY 8, 1944*

The following papers were presented:

**Congenital Vaginal Occlusion of the Cervix: Report of 2 Cases.** Walter T. Dannreuther, M.D. (For original article, see page 826.)

**Carcinoma Subsequent to Radiotherapy for Benign Uterine Conditions.** James A. Corscaden, M.D., John W. Fertig, M.D. (by invitation), and S. B. Gusberg, M.D. (by invitation).

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## THE OBSTETRICAL SOCIETY OF PHILADELPHIA

*MEETING OF FEBRUARY 3, 1944*

The following paper was presented:

**Supravescical Extraperitoneal Cesarean Section: A Review of the Anatomy and Technique, and Results in 250 Cases.** Edward G. Waters, M.D.

**PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY***MEETING OF FEBRUARY 7, 1944*

The following papers were presented:

Classification of Toxemia of Pregnancy. Paul Titus, M.D. (For original article, see page 817.)

Carcinoma of the Ovary. Samuel Goldstein, M.D. (To be published.)

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**BROOKLYN GYNECOLOGICAL SOCIETY***MEETING OF FEBRUARY 4, 1944*

The following paper was presented:

"John Osborn Polak, M.D." A Memorial Address. Alfred C. Beck, M.D.

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**Erratum**

In the article entitled "Caudal Analgesia: An Experimental and Anatomical Study," by Virginia Singleton Lanier, M.D., Howard E. McKnight, M.D., and Mildred Trotter, Ph.D., St. Louis, Mo., which appeared in the May issue, page 635, the positions of the outlines of the vertebral columns depicted in Fig. 1 should have read:

*"The letters A and B should have been interchanged."*

## Necrology

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WILLIAM SIDNEY SMITH, M.D., F.A.C.S., Diplmate of the American Board of Obstetrics and Gynecology, Graduate of the College of Physicians and Surgeons, New York, 1905, Chief Attending Gynecologist and Obstetrician of the Brooklyn Hospital, died suddenly on April 17, 1944, at the age of 61.

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